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CONTENTS OF PREVIOUS NUMBER

JULY 1948. NUMBER 1

North American Blastomycosis (Gilchrist's Disease):

I. A Study of the Disease from a Review of the Literature. Robert A. Starrs, M.D., Ottawa, Ontario, Canada.

II. An Analysis of Canadian Reports and Description of a New Case of the Systemic Type. Robert A. Starrs, M.D., and Max O. Klotz, M.D., Ottawa, Ontario, Canada.

Comparative Time Action of Globin Insulins. Joseph H. Rohr, M.D., and Arthur R. Colwell, M.D., Chicago.

Cardiac Amyloidosis: Electrocardiographic and Pathologic Observations. Stanford Wessler, M.D., and A. Stone Freedberg, M.D., Boston.

Myenteric Plexus in Congenital Megacolon: Study of Eleven Cases. Francis R. Whitehouse, M.D., and James W. Kernohan, M.D., Rochester, Minn.

News and Comment.

Book Reviews.

Archives of Internal Medicine

Volume 82 August 1948 Number 2

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ACUTE DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS

Report of a Case

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AND

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FROM TIME to time both clinicians and pathologists encounter cases of diffuse pulmonary fibrosis of undetermined origin. Generally, these cases are characterized by a protracted clinical course without distinctive features. The postmortem examination usually reveals a nonspecific chronic inflammatory process with extensive organization of the alveolar structures. In decided contrast to these, Hamman and Rich[1] described a group of 4 cases of pulmonary fibrosis in which both the symptoms and the anatomic findings were distinctive. The disease was usually of comparatively short duration, and the outstanding symptoms were those of weakness, increasing dyspnea, cyanosis and finally death in respiratory failure or failure of the right side of the heart. Even more striking than the clinical picture were the unusual anatomic findings. The lungs showed a diffuse, progressive proliferation of the alveolar connective tissue of a type not previously encountered either by them or by other observers.

The comparative rarity of such instances has no doubt contributed to the delay in their recognition. Hamman and Rich encountered 3 cases within the years 1931 to 1933, but almost ten years elapsed before a fourth case came to their attention. The detailed description of their experiences permitted Eder, Hawn and Thorn[2] to identify a puzzling case of theirs as belonging to the same group. Likewise, we found it comparatively easy to classify our case once we had become familiar with the reports of the previous authors.

From the Clinical and Laboratory Service of the B. S. Pollak Hospital for Chest Diseases, Medical Center.

1. Hamman, L., and Rich, A. R.: Acute Diffuse Interstitial Fibrosis of the Lungs, Bull. Johns Hopkins Hosp. **74**:177-212, 1944.

2. Eder, H.; Hawn, C. V., and Thorn G.: Report of a Case of Acute Interstitial Fibrosis of the Lungs, Bull. Johns Hopkins Hosp. **76**:163-171, 1945.

REPORT OF A CASE

The patient, a 33 year old white male printer, was in good health until April 1945. At that time he noticed that he tired easily and that he was gradually losing weight. Several months later cough, dyspnea and palpitation on exertion and easy fatigability developed, which required rest in bed from time to time. By October his dyspnea had become so severe that he was forced to give up working and was confined to bed almost constantly. At this time a roentgenogram of the chest (fig. 1*A*) showed a normal heart shadow and a peculiar haziness of the lower third of both pulmonary fields, somewhat more marked on the left. The electrocardiogram revealed sinus tachycardia. The internist who saw the patient was puzzled by the case but advanced the probable diagnosis of heart failure and sug-

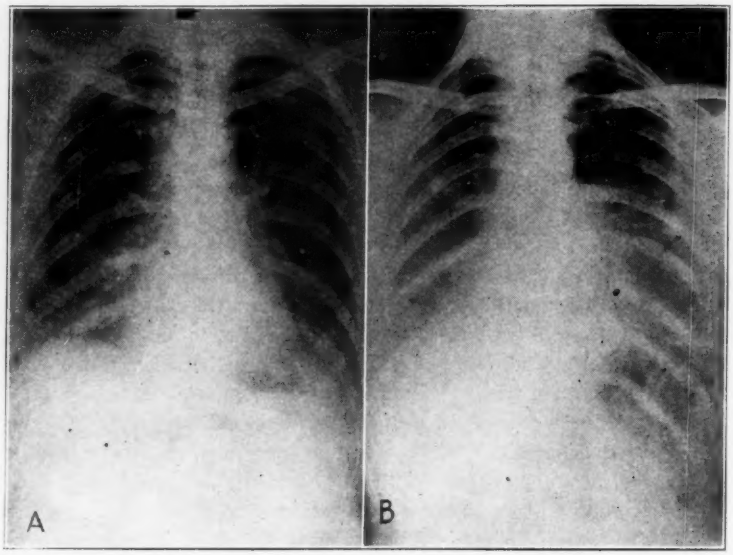

Fig. 1.—*A*, accentuation and increase of the pulmonary markings in both lungs, particularly those radiating into the lower lobes. In the latter there is a fine infiltrate most marked in the pericardiac regions. *B*, roentgenogram taken on the patient's admission to the hospital. Note increase in infiltration and extension into the midpulmonary fields. The infiltrate was so fine that it gave a "veiled" appearance to the lungs.

gested digitalization and diuretics. On November 7 he was seen in consultation by one of us (B.P.P.) because of the confusing clinical picture and the failure to respond to treatment. Hospitalization for further study was advised, and the patient was admitted to the Jersey City Medical Center on Nov. 9, 1945.

On admission to the hospital the physical examination revealed evidence of loss of weight, moderate dyspnea at rest, cyanosis and a rasping, esentially nonproductive cough. The heart sounds were rapid and regular. A soft systolic murmur was audible over the pulmonic area. There was no evidence of cardiac enlargement. The blood pressure was 119 systolic and 80 diastolic. The findings

in the lungs were remarkably few. There were scattered subcrepitant, inspiratory rales over the lungs anteriorly which disappeared on coughing. The liver was not enlarged. There was no edema of the extremities. Clubbing was not present. The temperature was elevated to 100.2 F. The roentgenogram on admission (fig. 1*B*) showed an extension of the process previously observed. The laboratory findings were all within normal limits. On November 30 the patient was transferred to our care at the Berthold S. Pollak Hospital for Chest Diseases.

Reexamination at this time indicated an extension of the disease as manifested by the notable dyspnea at rest and the increasing cyanosis requiring oxygen by mask intermittently. The examination of the lungs now revealed diminished percussion and moist rales over the lower half laterally and posteriorly. The blood pressure was 90 systolic and 48 diastolic. Repeated roentgenograms (fig. 2*A*) showed little change in the disease process in the lungs. The results of routine

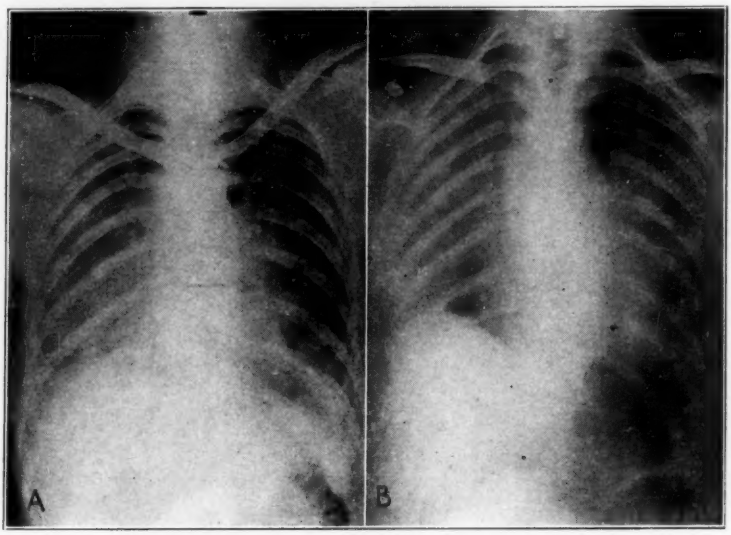

Fig. 2.—*A*, taken three days before the sudden rise in temperature from 100.2 to 104.0 F. and demonstrating the lack of change since the patient's admission. *B*, taken when the temperature rose to 104.0 F. The decided increase and extension of the process, sparing only part of the upper lobe of the left lung, are demonstrated.

laboratory examinations were within normal limits. The blood count revealed a hemoglobin content of 95 per cent (Sahli), 4,800,000 erythrocytes and 8,200 leukocytes, with a normal differential count. The chemical examination of the blood showed a nonprotein nitrogen content of 29.7 mg. per hundred cubic centimeters, a glucose content of 110 mg. and a total protein level of 7.1 mg., of which 4.8 mg. was albumin and 2.3 mg. globulin. The blood culture was sterile. The urine was normal. The reactions to Wassermann and Kahn tests were negative. Repeated examinations of the sputum and culture and bacteriologic study of the gastric washings did not reveal tubercle bacilli or fungi. The reaction to the tuberculin test was positive in a dilution of 1:100,000 (old tuberculin).

Penicillin aerosol therapy was tried and had to be discontinued when dyspnea and tachypnea required the patient to remain in an oxygen tent continuously. The cough could not be controlled by the usual sedative drugs. The temperature, which hovered around 100.2 F., suddenly rose on December 20 to 104.0 F. At this time roentgenologic examination (fig. 2*B*) showed considerable extension of the hazy appearance in the lungs on both sides so that only the apexes were relatively clear. Parenteral administration of 50,000 units of penicillin every three hours did not affect the fever. Several days later another roentgenogram (fig. 3) revealed complete involvement of both pulmonary fields. Tachycardia was marked at this time and was not influenced by digitalis. The patient died on December 26 with pronounced dyspnea and extreme cyanosis. Death was attributed to pulmonary insufficiency.

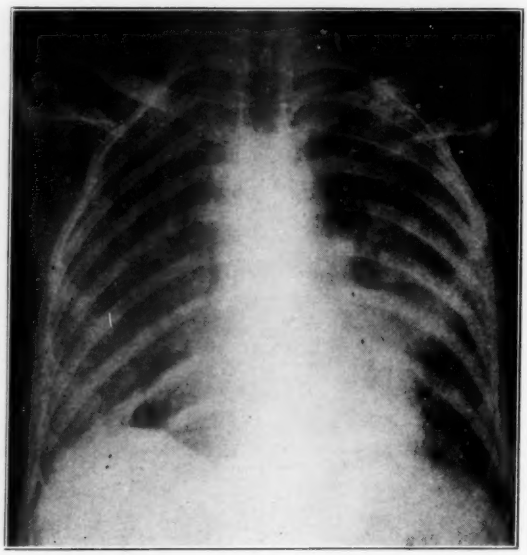

Fig. 3.—Involvement of both lungs just before death.

Anatomic Findings.—At autopsy the striking cyanosis noted clinically was observed. The essential gross abnormalities were limited to the heart and lungs; the remaining organs, aside from considerable cyanosis, were normal.

Heart: The organ weighed 300 Gm. The pericardium was smooth. The right auricle and ventricle were markedly hypertrophied and dilated. The left ventricle was of normal thickness and only slightly dilated. The myocardium of both ventricles was firm; no scars or other gross abnormalities were noted. The valves, endocardium and coronary arteries were normal. The great vessels were not unusual.

Lungs: The organs together weighed 1,940 Gm. They stood up well. The pleurae were smooth. No fluid was present in either hemithorax. On palpation the lungs were firm and for the most part solid and rubbery except for small areas

which were hypocrepitant. On section, an accentuation of the lobular markings was apparent throughout, together with a fine lacelike appearance (fig. 4). The cut surface was grayish red and smooth, with but small scattered areas of granular appearance. A mild degree of anthracotic stippling was seen throughout. On close inspection of the hypocrepitant areas, outlines of alveoli could be seen. The essentially smooth character of the cut surface was uniform in both lungs from apex to base. The trachea and the main and branch bronchi were patent, and their mucosae were slightly congested. Occasional branch bronchi contained a small

Fig. 4.—Cross section of the lungs. Note accentuation of all markings and smooth appearance.

amount of thick mucoid exudate. The tracheobronchial lymph nodes were small, soft and moderately anthracotic. The pulmonary arteries and veins were grossly normal.

Histologic examination of the lung revealed a picture that was fairly uniform in multiple sections from all lobes. The predominant feature was the pronounced thickening of the alveolar septums (figs. 5 and 6). The thickening was due to varying degrees of connective tissue proliferation. In addition, occasional alveolar septums were infiltrated with polymorphonuclear leukocytes and mononuclear cells.

At times edema of the alveolar walls was also present. The alveolar capillaries were widely dilated and congested. A second striking feature was the presence of a striking proliferation of alveolar epithelial cells, in some instances filling the entire lumen (fig. 7) or lining the walls in single layers, imparting a glandular appearance to the alveoli (fig. 8). Occasional epithelial giant cells were seen.

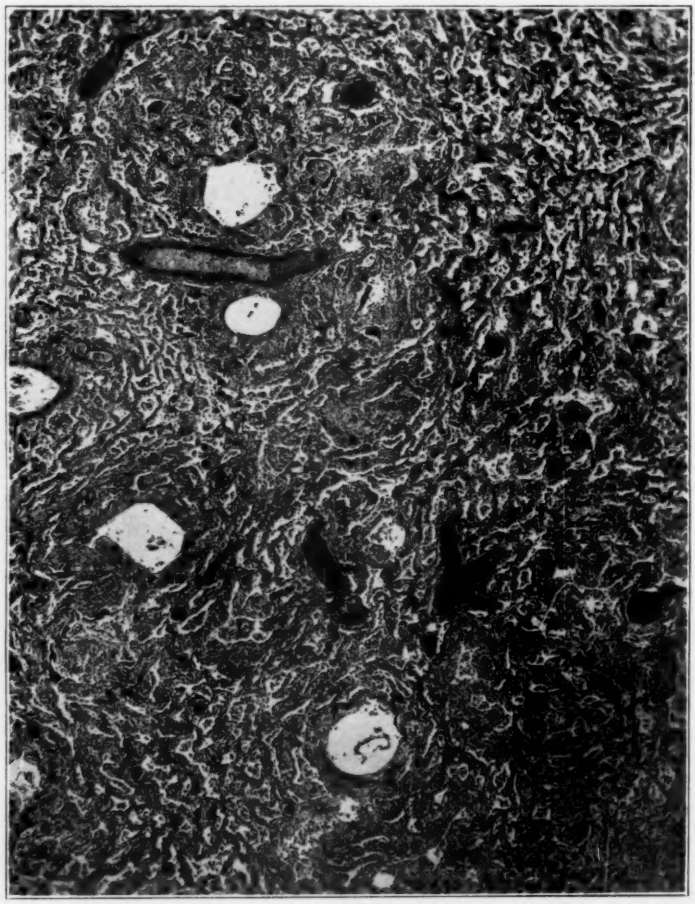

Fig. 5.—Diffuse character of the interstitial fibrosis in the lungs. Note the pronounced vascular congestion; low power magnification.

Scattered alveoli contained fibrin, and several showed connective tissue organization of the fibrinous exudate. Other alveoli were lined by a broad hyaline membrane (fig. 9). Many scattered alveoli contained vacuolated, mononuclear macrophages. Only a few small areas were present in which complete connective tissue organiza-

tion of the alveolar lumens had occurred, as commonly seen in chronic, organizing pneumonitis. The lobular septums were widened by connective tissue proliferation and edema. The bronchioles in some areas contained desquamated epithelial cells

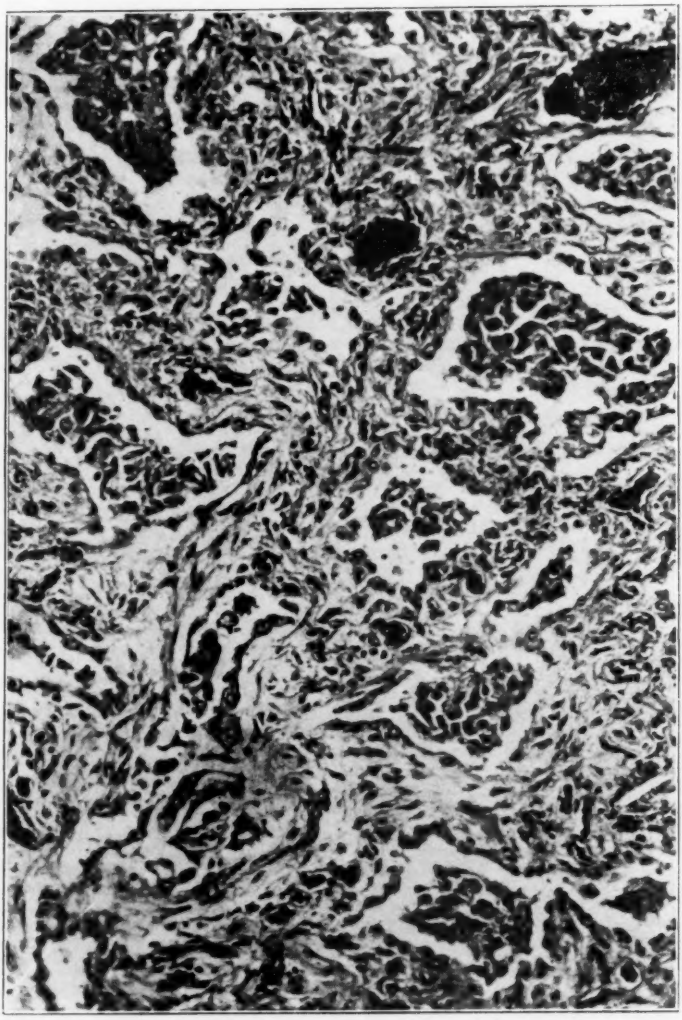

Fig. 6.—Pronounced connective tissue proliferation in the lungs, with notable widening of alveolar walls; medium power magnification.

and small amounts of exudate composed principally of degenerated polymorphonuclear leukocytes. Occasional bronchioles showed proliferation of the lining epithelium which at times assumed a transitional character, and in a rare bronchiole con-

nective tissue organization of the lumen was seen. The blood vessels were without significant alterations. Only occasional arteries showed elastica proliferation and reduplication of the elastica. Gram and Ziehl-Neelsen stains failed to reveal the presence of bacteria or fungi. Giemsa's stain did not show the presence of inclusion bodies in the epithelial cells.

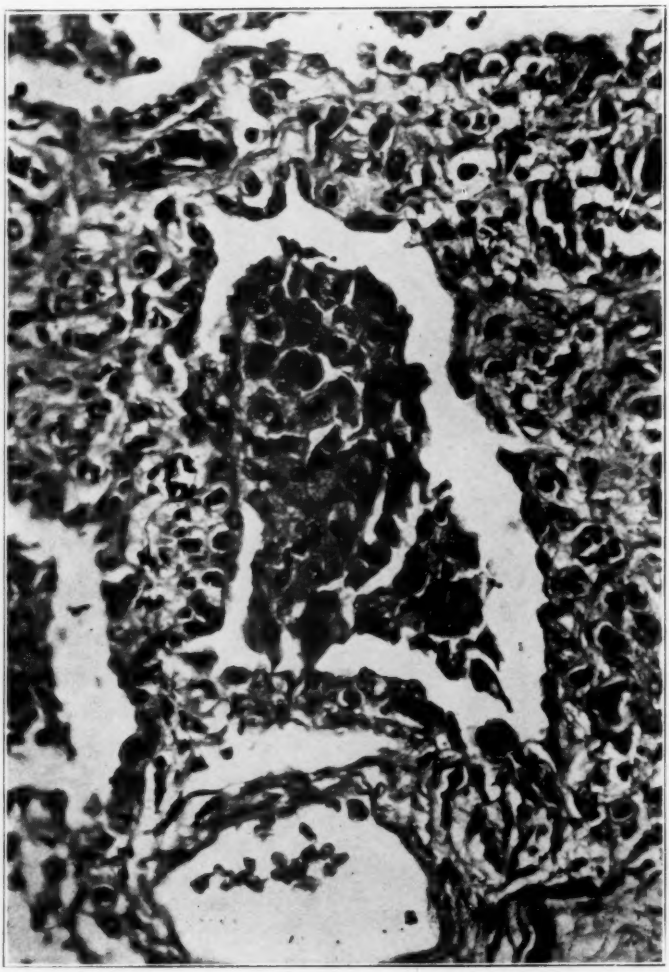

Fig. 7.—Alveolus in the lung containing a sheet of proliferated epithelial cells. Alveolar walls thickened by fibrous tissue growth; high power magnification.

The tracheobronchial lymph nodes showed only a moderate hyperplasia of the sinus endothelium and secondary follicles.

Other Organs: Results of microscopic examination of the remaining organs were not significant.

COMMENT

The clinical and anatomic findings in our case are in conformity in nearly all respects with those reported by the previous observers. These characteristic features permit ready identification of the cases despite their apparent rarity and support the contention of Hamman and Rich

Fig. 8.—Alveolar walls in the lung thickened by early connective tissue proliferation and edema. Note proliferation of alveolar epithelium imparting pseudogland appearance to alveoli; high power magnification.

that they represent a distinct entity. The lungs and the microscopic sections were shown to Dr. Paul Klemperer at the Mount Sinai Hospital, New York city. He stated that he had never observed a case of this type and was readily able to identify it from the description in the

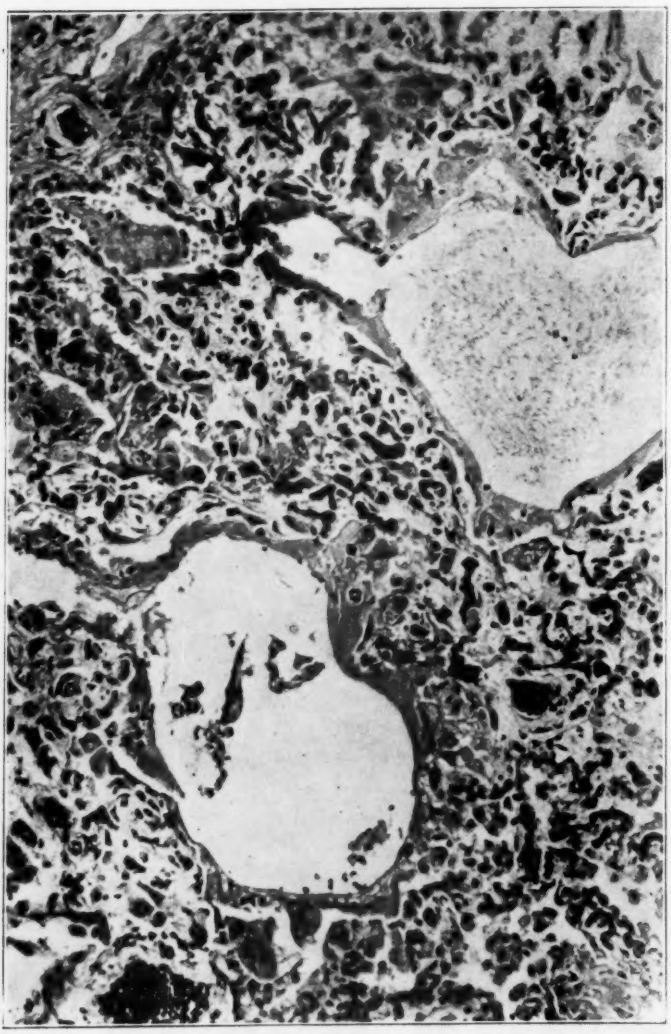

Fig. 9.—Alveolar lumens lined by hyaline membrane in the lung; medium power magnification.

publication of Hamman and Rich. The slides and the roentgenograms of the chest were also seen by Dr. Arnold Rich, who confirmed the diagnosis.

The origin of the clinical symptoms of progressive increase in dyspnea and cyanosis is readily understood in the light of the specific anatomic alterations in the alveolar walls. When these changes are far advanced and universal, as observed in the present case, lack of oxygen is severe and death in pulmonary insufficiency results. As might have been anticipated, an occasional instance of pulmonary osteoarthropathy is noted. This was described in the case of Eder, Hawn and Thorn.

Although in every case thus far reported there was advanced hypertrophy of the right side of the heart, in only 1 was failure sufficiently advanced to produce death. Apparently a fairly marked degree of hypertrophy of the right side of the heart may develop before frank cardiac failure is noted. This may be accounted for by the relatively short duration of the disease; pulmonary insufficiency hastens death before cardiac failure develops. Somewhat similar experiences have been described in cases of lymphangitic carcinosis of the lungs with obstruction to the pulmonary circulation.

The paucity of pulmonary signs on physical examination is striking in view of the subsequent anatomic findings. However, this may be explained by the fact that the lesion is predominantly interstitial in location. A fairly constant finding is that of harsh breath sounds. The presence of crackling and moist rales, together with intensified or distant breath sounds, may be due to the focal bronchopneumonia present in some instances in association with the interstitial fibrosis. The disparity between the physical findings and the roentgenographic appearance is not surprising since similar features have been noted in so-called atypical or virus pneumonia, a disease in which the anatomic lesion is also predominantly in the interstitial tissue, usually about the bronchi.

The gross appearance of the lungs is rather distinctive. The first impression gained is that the underlying process is that of an organizing pneumonitis. However, the fine, interlacing appearance of the section is unlike that usually seen in this condition. The histologic picture is characteristic. In the present instance the features are much like those described by Hamman and Rich in their second case, with the exception that we observed a striking proliferation of the alveolar epithelium. Since somewhat similar alveolar epithelial proliferation has been observed in cases of pneumonia associated with measles and whooping cough, Giemsa stains were made and searched carefully for the presence of cytoplasmic or intranuclear inclusion bodies; none was found. Our patient was exposed to various chemical compounds in the course of his work. These chemicals were obtained and subjected to careful toxi-

cologic analysis. However, nothing was found that could account for the changes in the lungs. As did the other authors, we have concluded that the cause is unknown. Any suggestions as to the cause at the present time would be purely speculative.

The course is rapid and fairly acute. The patients previously described were ill from periods varying from four to twenty-four weeks. As near as could be determined, our patient was ill for a total period of thirty-two weeks. While it is perhaps stretching the term "acute" a little too far to apply it to a disease with a course as long as thirty-two weeks, it would serve no purpose to replace it with the term "subacute." We prefer to retain the title originally introduced by Hamman and Rich so that others may become familiar with the reports in the literature and thereby perhaps aid in facilitating recognition of these cases.

SUMMARY

1. The term acute diffuse interstitial fibrosis of the lungs was introduced by Hamman and Rich to describe a comparatively rare group of cases characterized by an acute clinical course and terminating fatally.

2. The predominating symptoms are those of progressive dyspnea, cyanosis and a harassing nonproductive cough, with death in respiratory failure or in failure of the right side of the heart.

3. The pathologic features are those of diffuse fibrosis of the alveolar walls, with little involvement of the alveolar lumens.

4. The present report represents the third in the literature; a total of 6 cases have been described to date.

CLINICAL EXPERIENCE WITH NITROGEN MUSTARD THERAPY

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AND

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LOS ANGELES

RECENT reports of results obtained with the use of nitrogen mustard derivatives have aroused much speculation regarding the efficacy of chemotherapy in certain malignant neoplastic diseases. The Veterans Administration Hospital, West Los Angeles, Calif., has been designated as a center for the treatment of tumors. This provided a relatively large number of patients who had leukemias and lymphomas, and it was decided to evaluate the effects of nitrogen mustard therapy on a suitable group.

METHOD AND RESULTS

Method.—The routine study included a search for enlarged lymph nodes, examination of the liver and spleen, complete blood count, sternal puncture, roentgenologic study of the chest and biopsy. The patient was then presented to the members of a Tumor Board, who selected the type of therapy to be used in each instance. In those patients for whom the nitrogen mustard treatment was recommended, the bis form of the drug was administered intravenously, 0.1 mg. per kilogram of body weight, on alternate days until four injections had been given. Later it was found to be much more desirable to give the injections daily. The most recent change has been to increase the initial number to six, but the number of subsequent injections has been limited to four. The basic dose of 0.1 mg. per kilogram of body weight was adhered to throughout.

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The technic of administration was as follows: An intravenous infusion of 1 liter of isotonic sodium chloride solution was started. Ten cubic centimeters of isotonic sodium chloride solution was then injected into a bottle containing 10 mg. of the nitrogen mustard crystals. The required amount of the solution was then withdrawn in the dose of 1 cc. for each 22 pounds (10 Kg.) of body weight and injected immediately into the rubber tubing of the running sodium chloride infusion. Immediate injection is essential, since the nitrogen mustard is hydrolized and ineffective after a few minutes. Most patients will experience nausea and vomiting at some time after injection of the drug. These symptoms can be controlled most effectively by intravenous administration of "sodium amytal" in sufficient amounts to produce narcosis for the duration of the symptoms, which last for about four to six hours. Most of the patients

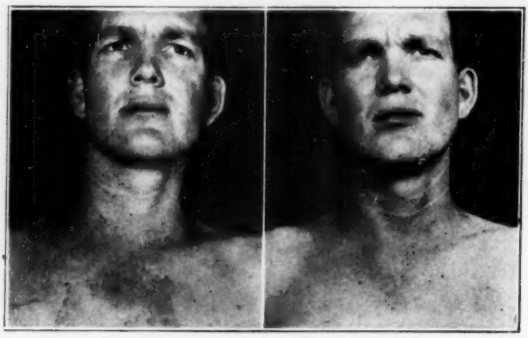

Fig. 1 (case 38).—Hodgkin's disease. Patient before and two weeks after the injection of nitrogen mustard.

experienced anorexia for the remainder of the day after injection; it therefore was found practical to administer the drug as late in the day as possible, since the appetite was usually normal by the next morning. Although no quantitative studies were made on this point, it appeared that the patient's strength and weight were better preserved when this plan was used. It was felt that the intravenous infusion of sodium chloride solution, although not necessary, reduced the incidence of thrombophlebitis as well as of nausea and vomiting.

Results.—Hodgkin's Disease: Seventeen patients for whom a diagnosis of Hodgkin's granuloma was made were treated. In 15 of these favorable response was observed at some time after treatment. A summary of the results observed in this group of patients is presented in table 1. Subjective improvement included an increased sense of well-being, a feeling of having greater strength and increased appetite. Objective improvement included decrease in the size of the tumor masses,

TABLE 1.—*Summary of Results in Hodgkin's Disease*

Case	Patient	Age	Date of Onset	Treatment (Dates of First Injections)	Period of Remission	Comments

TABLE 1.—*Summary of Results in Hodgkin's Disease*

Case	Patient	Age	Date of Onset	Treatment (Dates of First Injections)		Period of Remission	Comments
1	W.F.C.	31	November 1944	Nov. 14, 1946	(20 mg.)	2 wk.	There was slight subjective improvement and objective regression in the size of lymph nodes and spleen. Patient had several subsequent convulsions. Died Dec. 18, 1946; no necropsy
2	W.B.	40	March 1945	Jan. 11, 1947 March 3, 1947 April 14, 1947	(30 mg.) (20 mg.) (24 mg.)	3 wk. None None	First course: Subjective improvement and 1/3 reduction in size of spleen and lymph nodes; 5 day remission in fever. Preterminal before last two courses. Died April 19, 1947
4	K.StG.	22	August 1946	Dec. 28, 1946 Feb. 1, 1947	(24 mg.) (35 mg.)	2 wk. 2 wk.	Subjective improvement; lymph nodes regressed moderately and transiently. Second course cleared arm edema. Died March 3, 1947.
8	A.J.M.	32	April 1945	Feb. 5, 1947 April 1, 1947 June 14, 1947 Sept. 28, 1947	(22 mg.) (24 mg.) (35 mg.) (17 mg.)	5 wk. 8 wk. 6 wk.	Pronounced subjective improvement and regression in size of lymph nodes; limited regression of spleen. Nodes start reenlarging before symptoms recur
13	D.H.K.	29	May 1946	Feb. 20, 1947 April 17, 1947 June 16, 1947	(30 mg.) (30 mg.) (46 mg.)	6 wk.	Subjective improvement has persisted. Lymph nodes recurred in six weeks. Third course given to intensify effect of treatment before further remission
15	H.N.	48	August 1946	Feb. 26, 1947 May 17, 1947 July 28, 1947	(37 mg.) (32 mg.) (32 mg.)	6 wk. 4 wk.	Considerable subjective and objective improvement. The only recurrence has been that of pruritis, which responded to the first two courses but not to the third
18	A.R.S.	22	February 1947	March 24, 1947 June 14, 1947	(60 mg.) (45 mg.)	Indefinite Indefinite	No symptoms. Mediastinal mass had regressed to normal and shown no evidence of recurrence. Second course for intensive suppression only
19	W.F.S.	30	December 1946	April 9, 1947	(30 mg.)	Indefinite	No symptoms. Cervical mass regressed with treatment; this was followed by local roentgen ray therapy. No recurrence to date
22	G.W.M.	32	March 1946	April 16, 1947	(24 mg.)	4 wk.	Decided subjective and objective response. Treatment was not repeated, and patient died June 22, 1947
23	M.K.S.	45	1944	May 3, 1947	(24 mg.)	None	Patient in preterminal stage when treatment was initiated. No response. Died May 8, 1947.
24	E.J.	33	December 1946	May 5, 1947 June 19, 1947	(31 mg.) (31 mg.)	4 wk. 4 wk.	Considerable subjective and objective improvement. Temperature fell to normal in two days and remained normal for one month. Further treatment withheld because of tendency to marrow aplasia (noted before treatment)
30	G.J.	59	July 1943	July 1, 1947	(44 mg.)	12 wk.	Gastric resection in December 1943 showed Hodgkin's infiltration. Nephrectomy March 1947 also showed Hodgkin's disease. Now has pulmonary infiltration. Subjective improvement, with weight gain and slight regression of pulmonary lesion after treatment.
31	J.McH.	57	August 1946	June 23, 1947 July 22, 1947	(30 mg.) (20 mg.)	3 wk. 3 wk.	Patient in preterminal stage, but responded dramatically and was able to sit up after treatment. Visceral Hodgkin's disease without superficial splenomegaly or lymphadenopathy diagnosed on laparotomy and biopsy. Died Sept. 29, 1947.
32	LeR.B.	38	February 1946	June 20, 1947	(15 mg.)	None	Patient in preterminal stage when treatment started. Died June 24, 1947.
36	G.C.	58	May 1945	July 25, 1947	(36 mg.)	Indefinite	Subjective and objective improvement. Symptoms still in remission. Also has active pulmonary tuberculosis which was not intensified by nitrogen mustard
38	A.R.M.	23	January 1946	Aug. 1, 1947	(41 mg.)	Indefinite	Subjective and objective improvement. While still in remission, roentgen ray therapy was given to the neck, axillas and abdomen
40	Q.N.	27	January 1945	Sept. 12, 1947	(36 mg.)	Indefinite	Subjective and objective improvement. Symptoms still in remission

lymph nodes and spleen, remission of fever and gain in weight. Four patients (cases 1, 23, 31 and 32) were given their first course of treatment when it was apparent that their disease was preterminal. Three of these died soon thereafter, but 1 (case 31) improved sufficiently to get out of bed and sit up in a chair; he died four months after treatment was initiated. Three other patients died; 2 of these (cases 2 and 4) received definite but transient objective benefit from the nitrogen mustard though they continued their downhill course. The third (case 22) had a satisfactory remission for a month, when it was decided to administer roentgen ray therapy, to which he previously had responded fairly satisfactorily. The irradiation failed to halt the course of the disease at this time, and he died a month later. The photographs in figure 1 demonstrate the decrease in size of a cervical mass two weeks after the initiation

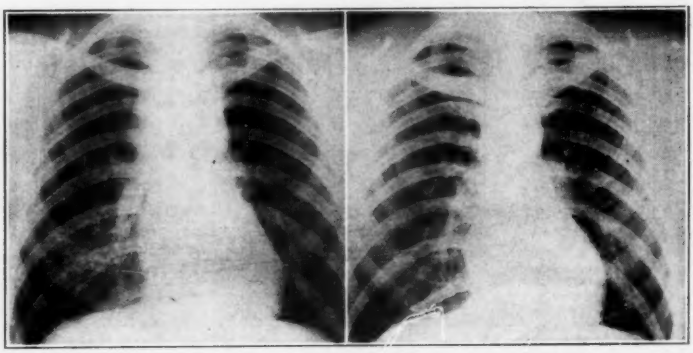

Fig. 2 (case 18).—Hodgkin's disease. Repression of a mediastinal mass two months after the initiation of nitrogen mustard therapy. There was further regression in the succeeding two months.

of therapy in a patient (case 38). This patient also had a massive abdominal infiltration which produced intestinal obstruction. This abdominal infiltration regressed, there was a remission of symptoms and there was a reduction in the size of the mass. In figure 2 may be seen roentgenologic evidence of a mediastinal mass before and two months after the initiation of therapy. The patient (case 18) was asymptomatic, and the enlarged mediastinal shadow was found by routine roentgenologic examination. In 1 case (case 15) the major complaint was intractable pruritis. The first two courses controlled this symptom for a period of a month each, but the third course was not effective. One patient (case 36) had Hodgkin's disease complicated by active bilateral pulmonary tuberculosis. A full course of nitrogen mustard therapy effectively controlled the Hodgkin's disease, and there was no evidence that the tuberculosis was affected in any way. The duration of the remissions is difficult

to assess. Patients in the earlier phases of the disease appeared to have suppression of signs and symptoms for about four months, while patients with late disease responded for only a week or two. The average period of remission seems to have been three or four weeks.

Lymphosarcoma and Reticulum Cell Sarcoma: Three patients with lymphosarcoma and 3 with reticulum cell sarcoma were treated. Four of these patients were in the preterminal stage when treatment was begun. Only 1 of these (case 5) responded with a transient reduction in the size of the lymph nodes; all 4 died. The condition of another patient (case 28) who had a large abdominal mass was improved. The

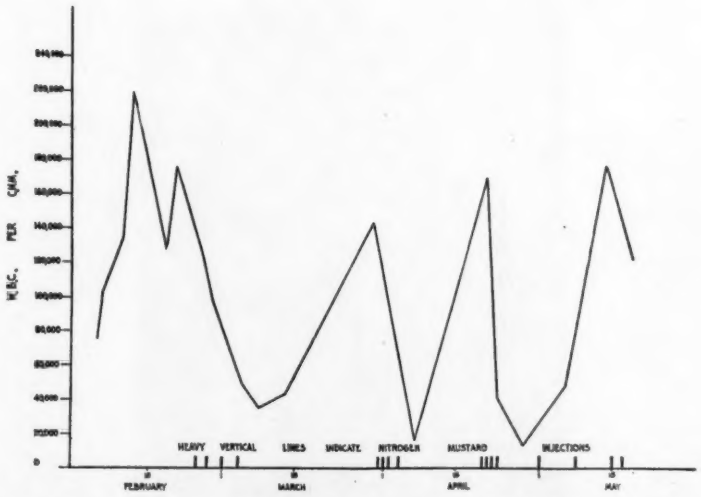

Fig. 3 (case 14).—Acute leukemia. Response of white blood cell count to injections of nitrogen mustard.

mass disappeared, and there was a reduction of radicular pain in the back. The mass recurred within two weeks, but the pain continued to be reduced. A second course of therapy was less effective, and the nausea and vomiting were so severe that a third course was refused. One patient (case 33) who had reticulum cell sarcoma responded well, but new nodes appeared three weeks after a course of treatment. Of the 6 patients, 5 are dead. In 3 cases there was some response, in 1 there was no effect on the course of the disease and in 2 there was remission for one to three weeks. The results observed in the patients are summarized in table 2.

Acute Leukemia: Five patients who had acute leukemia were treated. All five died. Two failed to respond; 1 demonstrated subjective improvement but no concomitant objective changes. One patient (case 6)

who appeared to be in the preterminal stage stabilized and survived for a period of two and one-half months. A similar patient (case 14), also apparently in the preterminal stage, who had generalized hemorrhages, hypertrophic gingivae, an enlarged spleen and a severe blastic leukocytosis, had a dramatic response, experiencing improvement subjectively and all the favorable objective changes previously described. Figure 3 illustrates his hematologic response. Thus, occasional patients experienced a transient remission after treatment, but the specific response could not be predicted in any case. The results observed in the treatment of these patients are summarized in table 3.

Fig. 4 (case 29).—Chronic myelogenous leukemia. Regression of spleen two weeks after nitrogen mustard therapy.

Chronic Leukemia: Two patients who had lymphatic leukemia and 4 who had myelogenous leukemia were treated. In each of the cases of lymphatic leukemia there was a decrease in the leukocyte count after treatment, although the number of cells did not reach levels lower than some observed in the same patients before treatment. One patient (case 7) who had an unsteady gait, slurred speech and difficulty in writing experienced a transient improvement which lasted for a period of two or three weeks; at necropsy leukemia infiltrations were found in the brain stem, and this condition was considered to be an adequate explanation for the signs and symptoms described. Two of the patients with

TABLE 2.—*Summary of Results in Lymphosarcoma*

Case	Patient	Age	Date of Onset	Treatment (Dates of First Injections)	Period of Remission	Comments
5	J. W.	29	July 1946	Nov. 28, 1946 (28 mg.)	None	Lymphosarcoma. Patient in preterminal stage. No subjective improvement but lymph node enlargement decreased. Marked aplastic anemia, with a white blood cell count of 150/c.mm. before therapy. Died Dec. 7, 1946.
12	A. A. W.	50	November 1946	Feb. 12, 1947 (26 mg.)	None	Reticulum cell sarcoma. Patient in preterminal stage. No objective or subjective improvement. Died Feb 25, 1947
16	C. B. B.	55	April 1946	March 12, 1947 (18 mg.)	None	Lymphosarcoma with terminal chronic lymphatic leukemia. Patient in preterminal stage. No subjective or objective improvement. Died March 21, 1947.
28	J. A. H.	55•	1942	June 3, 1947 (30 mg.) June 23, 1947 (30 mg.)	2 wk. 1 wk.	Lymphosarcoma. General improvement, with relief of radicular pain and intestinal obstruction. Abdominal mass 3″ in. diameter receded but recurred after two weeks. Pain did not return with full severity. Third course refused. Died Aug. 10, 1947
33	M. F.	53	December 1946	July 2, 1947 (41 mg.)	3 wk.	Reticulum cell sarcoma. Subjective and objective improvement; submandibular node decreased from 1½″ in. diameter until impalpable. Evidence of spinal metastasis and new nodes 3 weeks later.
39	W. G.	51	August 1946	Aug. 25, 1947 (36 mg.)	None	Reticulum cell sarcoma. Some subjective but no objective improvement. Patient in preterminal stage. Died Sept. 20, 1947

TABLE 3.—*Summary of Results in Acute Leukemia*

Case	Patient	Age	Date of Onset	Treatment (Dates of First Injections)	Period of Remission	Comments
6	F. B.	26	September 1946	Nov. 23, 1946 (28mg.)	4 wk.	Moderate subjective improvement. White blood cell count appeared to have stabilized. Patient later received a second course in another hospital, where a spontaneous leg abscess developed. Died Feb. 25, 1947
9	R. M.	39	November 1946	Feb. 3, 1947 (6 mg.)	None	The patient died suddenly on Feb. 9, 1947 before the effect of nitrogen mustard was apparent
10	J. A. P.	37	August 1946	Feb. 18, 1947 (10 mg.) March 12, 1947 (20 mg.)	None None	No objective or subjective improvement. Nitrogen mustard may have increased thrombopenia and hastened death. Died March 21, 1947
14	M. D.	37	December 1946	Feb. 24, 1947 (30 mg.) March 31, 1947 (28 mg.) April 20, 1947 (30 mg.) May 8, 1947 (30 mg.)	3 wk. 2 wk. 2 wk. None	Pronounced subjective and objective response, with improvement in gingival hypertrophy, skin hemorrhages and lymphadenopathy. Dramatic hematologic response. Life probably prolonged about 3 months. Patient died May 20, 1947
27	J. S.	25	February 1947	May 17, 1947 (25 mg.) June 9, 1947 (19 mg.)	None None	Subjective improvement after first course. Morbilliform rash after each course may have been due to nitrogen mustard. Death on June 11, 1947.may have been hastened by neutropenia Terminal proctitis

myelogenous leukemia experienced dramatic subjective and objective improvement; there was considerable reduction in the size of the spleen, and there was a fall in the leukocyte count. In 1 case (case 29) the count fell from 107,000 to 5,000 and in the other (case 37) from 150,000 to 12,000. The regression in the size of the spleen in case 29 is indicated in figure 4. Here again, the results were unpredictable. The response in cases of myelogenous leukemia was more favorable than that in cases of lymphatic leukemia. The duration of the remissions was three months. Results observed after the treatment of these patients are summarized in table 4.

Mycosis Fungoides: Two patients for whom a diagnosis of mycosis fungoides was made were treated. The first patient (case 20) responded

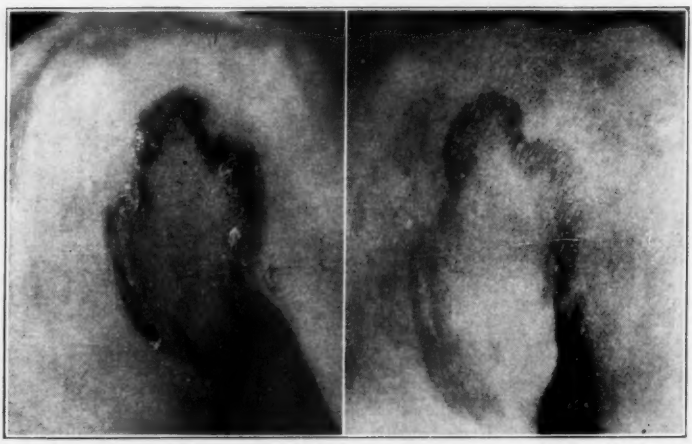

Fig. 5 (case 25).—Mycosis fungoides. Before and three weeks after the injection of nitrogen mustard.

satisfactorily after two courses of treatment. There was complete healing of the lesions for the first time within a period of eighteen months. Two weeks after a second course of treatment, a small blister appeared on the heel, the site of the most severe original lesion, and three weeks later this lesion consisted of a tumefaction 3 cm. in diameter and was surrounded by a local inflammatory reaction. This responded only slightly to the third and fourth courses of treatment. The second patient (case 25) also responded satisfactorily. The infiltrated lesions completely regressed, leaving only pigmented scars; the chronic exfoliative dermatitis was diminished, and there was relief from pruritis. The changes which took place may be seen in the photographs in figure 5.

TABLE 4.—*Summary of Results in Chronic Leukemia*

Case	Patient	Age	Date of Onset	Treatment (Dates of First Injections)	Period of Remission	Comments
7	O. P. S.	69	November 1944	Dec. 5, 1946 (35 mg.)	3 wk.	Lymphatic leukemia. Transient improvement in gait, speech and writing. White blood cell count fell from 26,000 to 9,000. Died March 6, 1947, after exploration of cerebellopontile angle tumor, which was found at necropsy to be a cyst of leukemic infiltrate
11	H. R. H.	52	April 1944	Feb. 18, 1947 (12 mg.) May 12, 1947 (24 mg.)	None None	Lymphatic leukemia. Questionable subjective improvement without change in splenomegaly or lymphadenopathy. Fall in white blood cell count no greater than normal variation
17	F. K.	23	December 1945	March 4, 1947 (34 mg.)	None	Myelogenous leukemia. No apparent subjective or objective response
26	O. B. M.	52	October 1944	May 18, 1947 (26 mg.)	None	Myelogenous leukemia. Patient preterminally went into a more acute phase of his leukemia and had diarrhea and septic course. Died May 22, 1947 before effect of nitrogen mustard could be noted
29	F. T.	58	August 1945	June 8, 1947 (39 mg.)	3 mo.	Myelogenous leukemia. Dramatic subjective and objective improvement. Spleen receded 6 cm. White blood cell count fell from 107,000 to 5,000 and was 12,000 two months after treatment. Died (of coronary arteriosclerosis and heart failure) Oct. 15, 1947
37	H. G.	57	September 1946	Aug. 1, 1947 (36 mg.)	9 wk.	Myelogenous leukemia and postoperative splenic flexure carcinoma. Slight subjective and moderate objective improvement. White blood cell count fell from 150,000 to 12,500

After three weeks the pruritis recurred, and after two months there were signs of reactivation in one lesion. A third course of treatment was administered, and the results were satisfactory.

Other Conditions: Several miscellaneous conditions were treated. In a patient who had polycythemia vera (case 21) there was no reduction in the erythrocyte count two months after a course of treatment consisting of the administration of 26 mg. At this time symptoms forced the use of phlebotomies, and 6 liters of blood was withdrawn. However, since the size of the spleen was diminished by one third, it is possible that the early fall in the red blood cell count was compensated for by the extrusion of red cells from the spleen. At present, six months after the course of nitrogen mustard and four months after the performance of the phlebotomies, the blood count is still well below its original level.

A patient (case 35) with pulmonary metastasis after orchidectomy for a teratoma of the testis had some symptomatic relief, i.e., increased well-being and reduction in obstructive edema of the leg, which lasted from two to three weeks. Another patient (case 34) with bronchogenic carcinoma reported similar symptomatic results and slight relief from bronchial obstruction. In a young man (case 3) who had chronic cervical reticuloendotheliosis there was a moderate regression in the size of the nodes, which lasted about three weeks, but there was no improvement in subjective symptoms.

Toxic Reactions: Toxic reactions were infrequent. In 1 patient a small vesiculation developed on the skin where a drop of the material accidentally fell. A second patient received a small amount of nitrogen mustard into the subcutaneous tissues of the antecubital fossa. The area was infiltrated with isotonic sodium chloride solution, and possibly this controlled the reaction. There was a resulting area of heat and tenderness which restricted the full range of motion. No necrotic reaction occurred, and the patient was then free of symptoms except for a slight paralysis of the ulnar nerve, which has now subsided. A moderately painful thrombophlebitis was noted in only 2 patients. Gastrointestinal symptoms were extremely common. Seventy per cent had vomiting, and 80 per cent had nausea from two to six hours after administration. After repeated courses of treatment, it appeared that the percentage of the patients who had these symptoms was much greater. Anorexia was an almost universal symptom and resulted in some weight loss during the course of treatment. No diarrhea was observed in this group of patients. The hematologic effect appeared to be limited principally to the leukocytes. The erythrocyte count was reduced gradually, which corresponded with the course of the disease rather than with the effect of the drug. The effect on the erythrocyte count was also obscured by frequent transfusions which were given to the patients. There was a definite numerical

decrease of leukocytes in all patients treated. The usual range of counts after treatment was 1,000 to 3,500, and this level was reached on about the tenth to the fourteenth day after the initiation of treatment. Return to normal levels generally occurred in the third or fourth week. Large areas of spontaneous suppuration developed in 2 cases. In a patient (case 2) who had acute aleukemic lymphatic leukemia an abscess developed in the right thigh. The leukocyte count dropped to as low a level as 1,500. This level was felt to be due to replacement with blast cells rather than to marrow aplasia. In another patient (case 4), who had Hodgkin's granuloma, large abscesses developed in both buttocks and over one scapula, which when drained yielded a pint or more (500 cc.) of pus each. His lowest leukocyte count was 3,600, of which 94 per cent was polymorphonuclear cells. Two patients had cutaneous eruptions which possibly were due to the nitrogen mustard. A patient (case 27)

TABLE 5.—*Source of Reported Cases*

September 1946	Goodman and Gilman (New Haven, Conn.)	7
	Wintrobe and McLennan (Salt Lake City)	34
	Dameshek (Boston)	16
	Goodman (Portland, Ore.)	10
October 1946	Jacobson, Spurr, Barron, Smith, Lushbaugh and Dick (Chicago)	59
February 1947	Alpert and Peterson (Washington, D. C.)	23
April 1947	Henstell and Tober (Los Angeles)	1
June 1947	ApThomas and Cullumbine (Manchester, England)	25
	Total	175

who had an acute lymphoblastic leukemia had a morbilliform rash on the sixth day after initiation of the first course and on the third day after the initiation of the second course of therapy. This rash appeared to be benefited by the use of antihistaminic drugs. However, he had been receiving penicillin as well, and sensitivity to this drug could not be excluded. Copper-colored macules developed in 1 of the patients who had Hodgkin's granuloma (case 31), resembling in character and distribution those of secondary syphilis. No other toxic reactions were noted.

SUMMARY OF PREVIOUS REPORTS

At the outset of this study, the published clinical experience with nitrogen mustard had been summarized in two articles describing its use in the treatment of 126 patients.[1] Later, Alpert and Peterson[2] reported

1. Goodman, L. S.; Wintrobe, M. M.; Dameshek, W., and McLennan, M. T.: Nitrogen Mustard Therapy, J.A.M.A. **132**:126 (Sept. 21) 1946. Jacobson, L. O.; Spurr, O. L.; Barron, E. S. G.; Smith, T.; Lushbaugh, O., and Dick, G. F.: Nitrogen Mustard Therapy, ibid. **132**:263 (Oct. 5) 1946.

2. Alpert, L. K., and Peterson, S. S.: The Use of Nitrogen Mustard in the Treatment of Lymphomata, Bull. U. S. Army M. Dept. **7**:187 (Feb.) 1947.

on 23 patients, most of whom had Hodgkin's disease, and Henstell and Tober[3] reported its use in a case of mycosis fungoides. Most recently, ApThomas and Cullumbine[4] reported treatment of 25 patients, bringing the total number of patients treated and reported on to 175. The source of this clinical material is summarized in table 5.

Hodgkin's Disease.—Among a group of 90 patients who received treatment for this disease improvement was noted in 84, or 93 per cent. Improvement included partial to complete disappearance of tumor masses, increased appetite, weight, strength and general well-being and absence of fever. The period of remissions varied; in some cases there was none and in others it lasted for eight months. Some patients previously found to be resistant to roentgen ray therapy became sensitive again. No study was made of the effect of the treatment on the ultimate life expectancy after the onset of the disease.

Lymphosarcoma and Reticulum Cell Sarcoma.—Twenty-five patients were treated, of which 22 were listed as having lymphosarcoma and 3 as reticulum cell sarcoma. In 14, or 56 per cent, there was indication of some improvement. The remissions were reported to last from two weeks to eighteen months. It was impossible to predict in advance what response might be expected, and several dramatic results were reported for patients in the terminal stage.

Acute Leukemias.—Nine patients were treated, and 3, or 33 per cent, experienced some favorable response. The duration of the remission is not given, but from the description of the cases it appears to have been a matter of days at most.

Chronic Leukemias.—Fourteen patients who had chronic lymphatic leukemia and 15 who had chronic myelogenous leukemia were treated. Of the group with lymphatic leukemia, 11, or 85 per cent, responded favorably, and of the group with myelogenous leukemia, 6, or 40 per cent, were improved. Again the response could not be predicted in advance. Remissions lasting up to twenty-one months were reported in cases of lymphatic leukemia and up to twelve months in cases of myelogenous leukemia.

Mycosis Fungoides.—One case was reported by Henstell and Tober, although 4 more are referred to in an editorial note. In this case there was a dramatic response, with satisfactory clearing of the lesion, but the remission was followed by the authors for only one month. More recently ApThomas and Cullumbine[4] reported a case in which there was no response.

3. Henstell, H. H., and Tober, J. N.: Treatment of Mycosis Fungoides with Nitrogen Mustard, J. Invest. Dermat. **8**:163 (April) 1947.

4. ApThomas, M. I. R., and Cullumbine, H.: Nitrogen Mustards in Hodgkin's Disease, Lancet **1**:899 (June 28) 1947.

Miscellaneous Conditions.—The remaining 20 cases fall into several diverse categories. Three patients with giant follicle lymphoma were treated, and all responded with diminution in the size of the lymph nodes although the clinical course continued unaltered. Five patients who had polycythemia vera were treated, and all responded with a remission of three to six months' duration; in 1 case the remission continued for over twelve months. These patients were subjected to phlebotomies often enough to bring the erythrocyte count to normal levels before the nitrogen mustard was administered, and the remission was interpreted as the period during which this count remained normal. Unpredictable relief

TABLE 6.—*Comparison of Results with Reported Results*

Diagnosis	Patients Reported on			Wadsworth General Hospital Patients				
	Total	Improved	%Improved	Total	Improved	%Improved	Dead	% Dead
Hodgkin's disease	90	84	93	17	15	88	7	41
Lymphosarcoma including reticulum cell sarcoma	25 (3)	14	56	6	3	50	5	83
Acute leukemia	9	3	33	5	2	40	5	100
Myelogenous leukemia	15	6	40	4	2	50	2	50
Lymphatic leukemia	14	11	86	2	1	50	1	50
Mycosis fungoides	2	1	50	2	2	100	0	0
Polycythemia vera	5	5	100	1	1	100	0	0
Miscellaneous (bronchogenic carcinoma, teratoma of testis, chronic reticuloendotheliosis, giant follicle lymphoma, sympathoblastoma, multiple myeloma and others)	15	11	--	3	3	--	1	--
Totals	175	--	--	40	--	--	21	--

of symptoms without concomitant objective improvement was produced frequently in cases of various malignant growths, especially bronchogenic carcinoma.

Toxic Reactions.—The most common local reaction appears to have been thrombophlebitis. This was most prevalent after the use of the tris compound and has been much reduced by the use of the bis compound. Nausea and vomiting were universal, and each group had its own method of treatment, no one of which was completely effective. There were concomitant anorexia and loss of weight. However, there was no report of serious diarrhea. The formed elements of the blood were persistently depressed for a period of two to four weeks. No fatal in-

5. Gilman, A., and Philips, F. S.: The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides, Science **103**:409 (April 5) 1946. Rhoads, C. P.: Nitrogen Mustards in the Treatment of Neoplastic Disease, J.A.M.A. **131**:656 (June 22) 1946.

fection was reported, in spite of counts as low as 200 leukocytes per cubic millimeter. All patients who survived sufficiently long appeared to have made a satisfactory recovery. No toxic rashes were reported.

COMMENT AND CONCLUSIONS

The theoretic backgrounds of the use of nitrogen mustard have been discussed in considerable detail by other authors,[5] although even now the exact mechanisms of action are not well known. A complete survey of the clinical results following the treatment of approximately 2,000 patients is to be presented by the Committee on Atypical Growth of the National Research Council. In this report our aim has been to present the results observed in the treatment of a group of patients and to correlate these results with those reports already published.

In general, this group of patients has reacted both qualitatively and quantitatively in close parallel with patients in the reported cases. The greatest discrepancy was that prolonged remissions, reported by others, were not observed by us. The incidence of response in our patients is as close to the reported results as the small size of the group would permit. It is possible that some of the earlier patients in this study might have responded if it had been realized that a significant fall in the leukocyte count was a necessary index of the adequacy of dosage.

Experience has demonstrated that when the drug is given in the recommended dosages the toxic effects are not to be feared. The local reactions of cutaneous vesiculation, extravasation and thrombophlebitis usually can be avoided by care and proper technic. The use of an infusion of sodium chloride solution avoids extravasation and reduces thrombophlebitis to a minimum. Nausea and vomiting can be reduced by adequate sedation and by administration late in the day. The effect on the bone marrow appears to be related to the therapeutic effect, and no patient has failed to recover from leukopenia except when this condition was a part of the primary disease. A total dose of 0.8 to 1.0 mg. per kilogram of body weight, given in one course, is reported to be the critical level at which severe and prolonged aplasia is initiated.

Nitrogen mustard appears to offer promise of almost certain remission in Hodgkin's disease and polycythemia vera. Lymphosarcoma, reticulum cell sarcoma, chronic leukemia and mycosis fungoides respond in slightly more than one half of the cases, but such a result cannot be predicted in advance. The response of the other diseases appears to be less consistent, and the group of patients described in this report is too small to permit conclusions of a general nature. The earlier the clinical state of the disease, the more likely is the remission to be clinically significant and the more possible the restoration of the patient to social and

economic usefulness. For diseases in which nitrogen mustard has proved occasionally useful, one course may be tried to determine the patient's response. This should be done for the remission itself and to defer the development of resistance to roentgen rays. Since the first adequate course of nitrogen mustard, judged by the hematopoietic response, appears to be the most effective, failure to respond to the first course obviates the necessity of repeating treatment. Recently, several research groups have begun to study the effects of nitrogen mustard when combined with roentgen ray therapy. It is hoped that this will prolong the duration of the remissions. The rapid response to the drug complements the slower but more prolonged effects of roentgen rays, and this in itself is of value.

SUMMARY

1. Forty male patients who had Hodgkin's disease, lymphosarcoma, leukemia and related diseases were treated with bis-beta-chloro-ethylamine hydrochloride (nitrogen mustard).

2. The results observed in this study are similar, both quantitatively and qualitatively, to those summarized from reports in the literature.

3. Nitrogen mustard appears to be an effective drug in the treatment of Hodgkin's disease, and in some cases of lymphosarcoma, leukemia, mycosis fungoides and polycythemia vera. It appears to offer symptomatic relief in some instances of terminal and metastatic carcinoma of diverse origin.

4. The therapeutic application of the drug results in a prompt response which is more rapid than that which occurs after roentgen ray therapy, but the remission produced is of much shorter duration.

5. No serious toxic reactions were encountered.

6. The theoretic implications of a chemical which can reduce the size of certain tumors or the magnitude of a leukocyte count within a period of a few days, even if the effect is only transient, is of greater significance than the therapeutic applications which have been explored up to the present time.

OSTEOPETROSIS

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OSTEOPETROSIS (Albers-Schönberg's disease) is a rare malady of unknown causation. Little more than 150 cases have been reported in the literature since its discovery in 1904 by a German roentgenologist, Albers-Schönberg.[1] Many names have been used to describe it, notably marble bones,[2] chalky bones,[3] osteopetrosis[4] and osteosclerosis fragilis generalisata.[5] Some authors have erroneously attributed the earliest description of this disease to Heuck,[6] who in 1879 described a condition similar to osteopetrosis, now known to be myelofibrosis.[7] Both diseases present bone marrow fibrosis, hepatosplenomegaly and generalized lymphadenopathy. However, as one can glean from the name, marble bones, the osseous system in this condition is merely abnormally dense, whereas in myelofibrosis one sees a shotty infiltration of the marrow, which may be sclerotic or lytic in nature.

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1. Albers-Schönberg, H.: (*a*) Röntgenbilder einer seltenen Knochenerkrankung, München. med. Wchnschr. **51**:365, 1904; (*b*) Eine bisher nicht beschriebene Allgemeinerkrankung des Skelettes im Röntgenbild, Fortschr. a. d. Geb. d. Röntgenstrahlen **11**:261-263, 1907.

2. Alexander, W. G.: Report of a Case of So-Called "Marble-Bones," with a Review of the Literature and a Translation of an Article, Am. J. Roentgenol. **10**:280-301, 1923.

3. Pirie, A. H.: The Development of Marble Bones, Am. J. Roentgenol. **24**:147-153, 1930; Marble Bones, ibid. **30**:618-620, 1933.

4. Karshner, R. G.: Osteopetrosis, Am. J. Roentgenol. **16**:405-419, 1926.

5. Davis, G. B.: Osteosclerosis Fragilis Generalisata, Arch. Surg. **5**:449-463 (Nov.) 1922.

6. Heuck, G.: Zwei Fälle von Leukämie mit eigenthümlichen Blut-resp. Knockenmarksbefund, Virchows Arch. f. path. Anat. **78**:475-496, 1879.

7. Rosenthal, N., and Erf, L. A.: Clinical Observations of Osteopetrosis and Myelofibrosis, Arch. Int. Med. **71**:793-813 (June) 1943.

Osteopetrosis has no predilection for age or sex, being seen about equally distributed between male and female patients;[8] the disease has been reported in aged persons[4] and even in utero.[9] The symptoms are decidely different in children and in adults, which has led some physicians to consider the condition to exist in two forms, malignant and benign.[10] In young persons the severity seems much greater than in older persons, frequently eventuating fatally. The older patient may be asmyptomatic and his illness often discovered by accidental roentgenographic examination.

SIGNS AND SYMPTOMS

The outstanding feature of the disease is the high incidence of fractures following trivial injury. Fortunately, they usually heal without difficulty, although in some patients delayed union or nonunion occurs, and the incidence of osteomyelitis at these fracture sites is higher than normal.[8] Commonly one sees delayed dentition and dental caries which often lead to abscesses and osteomyelitis of the jaw. It is believed that the bones are less resistant to infection as a result of the dense bony overgrowth which crowds out protective vascular elements.[11] This is a serious complication and may lead to death or remain as a chronic indolent infection.

Frequently one sees hepatosplenomegaly and generalized lymphadenopathy associated with severe anemia, a common observation in infants. Often the patient complains of loss of sight, deafness or paralysis of muscles supplied by cranial nerves, all attributed to narrowing of the cranial foramens with resultant nerve atrophy. Hydrocephalus is common in children.[8] It is believed that the small cranial foramens produce increased intracranial pressure by obstructing venous outflow. Another explanation is that the vascular distention causes hemorrhage, with formation of a chronic subdural hematoma.[12]

REPORT OF A CASE

L. W., an unmarried white woman, aged 37, was first seen at the surgical outpatient clinic in November 1946, complaining of headache, lightheadedness and multiple contusions following a fall five days previously.

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8. Péhu, M.; Guichard, A., and Jeune, M.: La maladie des os de marbre et les syndromes marmoréens, J. de méd. de Lyon **27**:173-200, 1946.

9. Jenkinson, E. L.; Pfisterer, W. H.; Latteier, K. K., and Martin, M. E.: A Prenatal Diagnosis of Osteopetrosis, Am. J. Roentgenol. **49**:455-462, 1943.

10. McPeak, C. N.: Osteopetrosis: Report of Eight Cases Occurring in Three Generations of One Family, Am. J. Roentgenol. **36**:816-829, 1936.

11. Winter, G. R.: Osteosclerosis Fragilis (Albers-Schönberg's Disease): Two Cases, Am. J. Orthodontics **31**:637-649, 1945.

12. McCune, D. J., and Bradley, C.: Osteopetrosis (Marble Bones) in an Infant: Review of the Literature and Report of a Case, Am. J. Dis. Child. **48**: 949-1000 (Nov.) 1934.

Questioning revealed that she had a chronically draining right ear, the discharge from which had become bloody since the fall, but this did not seem unusual to her since, as she stated, this always happened when she had a "cold," as was the case at the time of examination.

The personal history revealed nothing of significance except for a mastoid infection on the right side eighteen years prior to examination. This had been

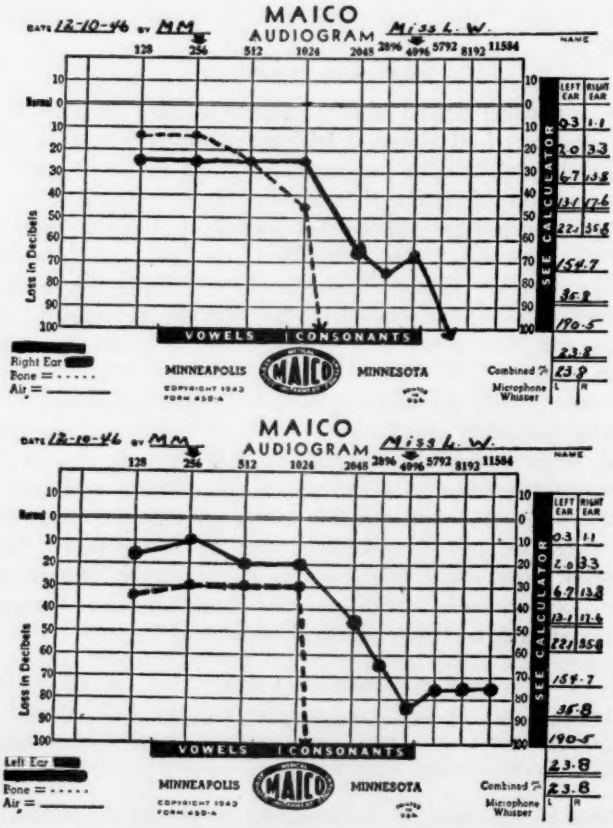

Fig. 1.—Audiograms of both ears, showing decided loss of both bone and air conduction above 1,024 double vibrations, indicative of inner ear deafness. The upper audiogram is of the right ear, and the lower audiogram is of the left ear.

accompanied with mild progressive deafness during the past ten years. There was no recollection of any fracture.

The family history likewise revealed nothing of importance. She was an only child. There was no knowledge of parental consanguinity, of maternal abortions or of any bone disease in any relatives.

Physical examination showed a dull lethargic well developed white woman, who appeared to be her stated age. The pulse rate and respirations were normal; the temperature was 96 F. and the blood pressure 115 systolic and 60 diastolic.

The eyes were normal as to pupillary size and reaction, fundi and visual fields. The right ear drum showed multiple scarring and a perforation in the posterior inferior quadrant. The Weber test elicited lateralization to the right. Audiograms (fig. 1) confirmed that deafness was present, with a total loss of hearing of 23.8 per cent—35.8 per cent in the right ear and 22.1 per cent in the left.

The type of curve was characteristic of an inner ear deafness, with loss in the higher frequencies. The remainder of the physical examination was noncontributory.

Psychologic examination revealed the patient to be lacking in initiative and rather self conscious. She had prepared herself to become a teacher, but had never become active in this work. Her service in the government for the past three years had been acceptable. Socially she was a quiet retiring person who had few friends and spent most of her time reading. At times she felt "despondent and blue." The fact that her mother had been confined to a mental institution for the past thirty years was a source of concern to her, with respect to her own future.

In talking with her it was evident, even allowing for her deafness, that she was dull, bewildered and slow in responses. She seemed to have difficulty comprehending directions and took a passive attitude, with little show of emotional responsiveness. At times she appeared mildly depressed, but for the most part her emotional reactions were shallow and apathetic. Psychologic testing showed her to have average intelligence, with some limitation in comprehension and concentration. Personality tests indicated limitation of emotional drive and responsiveness.

It was felt that there were definite disturbances in this woman's emotional reactions and personality makeup. It was difficult to tell whether these were of recent origin or had existed for many years. It was indicated that she was limited in her effective adjustment to life, that she lacked initiative in her work and that she had limited social participation. The personality picture suggested schizoid characteristics.

Laboratory Studies.—The urine was normal except for the observation of Trichomonas vaginalis. Examination of the blood revealed 4,300,000 red blood cells, 8,050 white blood cells and hemoglobin 12.5 Gm., or 86 per cent (Sahli). The cell volume was 44 per cent, or 104 per cent of normal. The color index was 1.0, the volume index 1.2 and the saturation index 0.81. The mean cell volume was 102 cubic microns, the mean cell hemoglobin 29 micromicrograms and the mean cell hemoglobin concentration 28 per cent. The differential count revealed 30 per cent lymphocytes, 4 per cent monocytes, 63 per cent neutrophils, 3 per cent eosinophils and 239,000 and 250,000 platelets. Kahn and Mazzini reactions were negative. The sedimentation rate was 11 mm. (Cutler) per hundred cubic centimeters. In the fragility test, the patient's beginning hemolysis was 0.44 per cent sodium chloride and complete hemolysis 0.34 per cent sodium chloride, with the control showing beginning hemolysis 0.44 per cent sodium chloride and complete hemolysis 0.34 per cent sodium chloride. The prothrombin time of the patient was 12 seconds, or 80 per cent, and the control 15 seconds. Nonprotein nitrogen was 34.0 mg. per hundred cubic centimeters. The cholesterol was 148 mg. and the calcium 11.8 mg. per hundred cubic centimeters. Inorganic phosphorus was 2.8 and alkaline phosphatase 2.8 Bodansky units. The basal metabolism rate was — 12 per cent.

Roentgenologic Studies.—In the skull (fig. 2) there was a decided increase in density of the base and decided thickening of the bones of the cranial vault, with

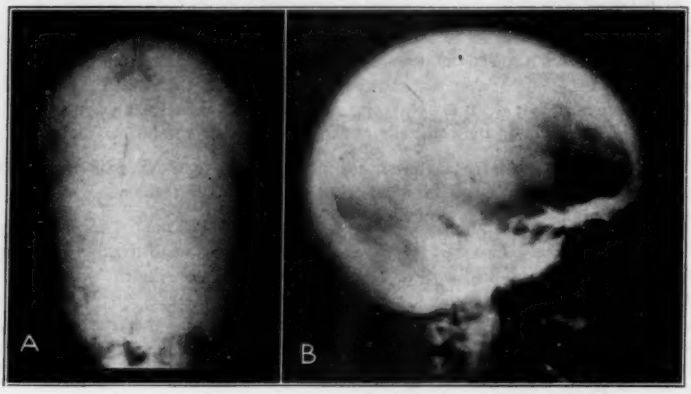

Fig. 2.—*A*, thickening of the cranial vault, indicating that intramembranous ossification was also affected. *B*, extraordinary denseness of the base of the skull and associated posterior clinoid "clubbing."

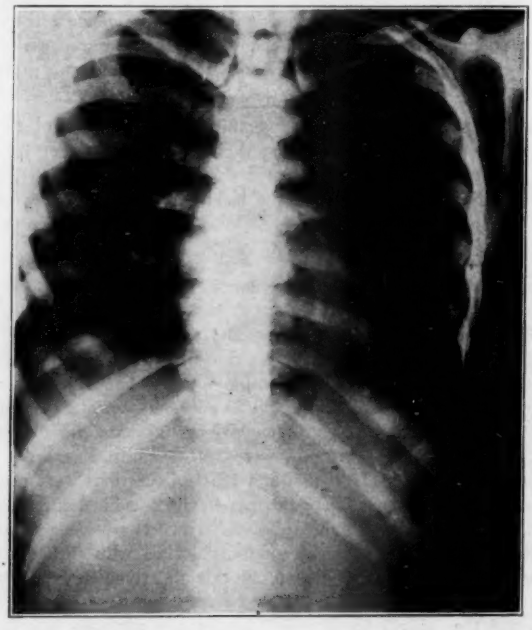

Fig. 3.—Roentgenogram of the thoracic aspect of the spine, showing the extreme calcification of the vertebrae.

no differentiation between the outer and inner tables and total effacement of the diploic portion. The petrous portions of the temporal bones were decidedly dense,

and no mastoid air cells could be differentiated. The sella turcica was well formed, but the posterior clinoids were thickened, with bulbous clublike extremities. Both sides of the mandible manifested hypermineralization but there was still some semblance of trabeculation discernible.

Fig. 4.—Roentgenogram of the pelvis, showing the decided density of all bones except the iliac crests where there was a tendency to osteoporosis.

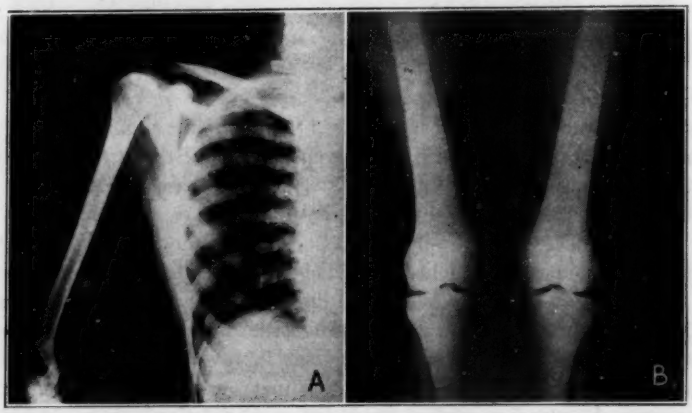

Fig. 5.—Roentgenograms of the humerus (*A*) and the femurs (*B*), showing the tendency toward thickening of the upper third of the humerus and the lower part of the femurs.

The ribs, the dorsal and lumbar portions of the spine (fig. 3) and the upper halves of both humeri showed involvement similar to the changes in the mandible.

There was also the same type of hypermineralization, but with defacement of normal architecture, in the bones of the pelvis (fig. 4) and in both femurs (fig. 5). The upper halves of the tibias and fibulas were similarly involved, and these bones showed some lack of normal modeling or tubulation.

CAUSATION OF OSTEOPETROSIS

In osteopetrosis so many factors have been considered as causal agents and with such frequency that none can be omitted. The most prominent factor is heredity. The high incidence of the disease in parents and grandparents of patients suffering from the disease and the

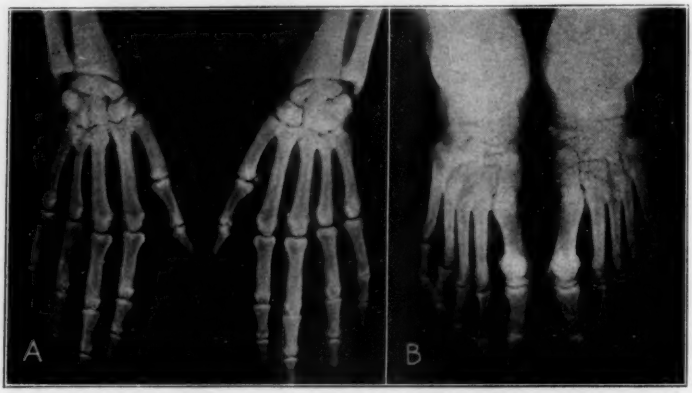

Fig. 6.—Roentgenograms of the hands (*A*) and the feet (*B*), revealing the generalized hypermineralized condition of bone.

presence of the condition in infants and young children cannot be overlooked. McPeak[10] reported the occurrence of the disease in 8 members in three generations of one family. Pirie,[3] Higinbotham and Alexander[13] and, most recently, Kelley and Lawlah[14] have reported occurrence in 1 or more members of a family. That some hereditary factor, regarded by most authors as a mendelian recessive trait, is at play seems probable.

Inasmuch as the osseous and the hemopoietic systems have a common origin, an undifferentiated mesenchyme, it would seem probable that the pendulum could swing either way in favoring growth of these two systems. Thus, when the primitive marrow cavity is formed and blood vessels, carrying with them undifferentiated tissue, grow in from

13. Higinbotham, N. L., and Alexander, S. F.: Osteopetrosis: Four Cases in One Family, Am. J. Surg. **53**:444-454, 1941.

14. Kelley, C. H., and Lawlah, J. W.: Albers-Schönberg Disease: A Family Survey, Radiology **47**:507-513, 1946.

the periosteum, there is the inherent power present for this tissue to develop into osseous or hematogenic elements. In this case osteogenesis is favored at the expense of the hemopoietic system. On the opposite balance of the scale is offered osteogenesis imperfecta as an example of decreased bone production. In this condition, the bones are narrow and rarefied and the individual trabeculae are thin. This disease is believed to be hereditary in nature and, like osteopetrosis, has been diagnosed in utero. Another interesting analogy between these two diseases is that both present an early fulminating type, the so-called malignant type, that develops early in life with such devastating effects and a latent much less severe type, the so-called benign form, that appears to start, or at least is discovered, in adults.

In 1936 Spéder,[15] having discovered osteopetrosis in a Moroccan native, was impressed with its similarity in regard to bony changes to a disease in animals known as "darmous," which occurs in areas where the drinking water contains small quantities of fluorides and phosphorus. It is known that osteomyelitis of the mandible and late, as well as faulty, dentition associated with dental caries are common symptoms of both osteopetrosis and chronic fluorosis. Therefore, Spéder made roentgenologic studies of the skeletons of 6 such natives presenting severe dental disturbances and observed in all bony changes similar to osteopetrosis.

Bishop[16] in the same year made a complete roentgenologic study of the bony changes in a human being suffering from chronic fluorine poisoning and thirteen and a half months later was fortunate enough to secure a postmortem study of this person. The essential roentgenographic changes he reported were an increase in bone density, with no alleviation in bone structure, lack of normal sharpness of bone outline and extension of calcification into ligamentous attachments. On subsequent microscopic study the haversian canals were observed to be plugged with calcium fluoride crystals. The chemical analysis of segments of the various bones and neighboring deposits showed a fluorine content that varied from 0.29 to 0.68 per cent (method of Willard and Winter). The bones showing the highest fluorine content were the densest roentgenographically. Normal fluorine content of bone is 0.03 to 0.07 per cent of fluorine.

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15. Spéder, E.: L'ostéopétrose généralisée ou "marmoskelett" n'est pas une maladie rare: Sa fréquence dans l'intoxication flourée, J. de radiol, et d'electrol. **20**:1-11, 1936; abstracted, Am. J. Roentgenol. **38**:506, 1937.

16. Bishop, P. A.: Bone Changes in Chronic Fluorine Intoxication, Am. J. Roentgenol. **35**:577-585, 1936.

The studies by Kramer and his co-workers[17] and Clifton and his co-workers[18] show that the bones in patients with osteopetrosis contain only normal chemical constituents, with merely a higher carbonate content associated with hypermineralization. Furthermore, there is individual trabecular thickening and numerical increase, with loss of normal architecture not seen in chronic fluorosis. Also, the extension of calcification to soft tissue, ligaments and cartilage, seen only in the latter, is a further differential feature.

Though all glands of internal secretion have been incriminated at one time or another, perhaps the only one which might bear some relationship to osteopetrosis is the parathyroid. A great deal of interest was aroused over this possibility when Péhu and his co-workers[19] observed a parathyroid adenoma in their patient with osteopetrosis.

In 1932 Selye,[20] who administered parathyroid homone experimentally to rats over a prolonged period of time, made some interesting observations. At first he noted the typical signs of osteitis fibrosa cystica, with the usual outpouring of osteoclasts, bony decalcification and resorption, marrow fibrosis and associated mobilization of calcium. This was followed, however, by a secondary stage of osteoblastic proliferation, beginning at the metaphysis and resulting in a dense bony overgrowth which was strikingly similar to that seen in osteopetrosis.

Furthermore, he observed that this primary phase of osteoclasis and calcium mobilization could be omitted if he gave small doses of parathyroid hormone, the rats showing signs of osteoblastic activity only.

Along similar lines, Pugsley and Selye[21] studied the effects of 20 units of parathyroid hormone, administered daily, on the calcium levels in the blood and urine, as well as associated osteoclastic and osteoblastic activity. They observed that when the maximum number of osteoclasts was present, the levels of calcium in the blood and the urine reached their peak and that as the osteoclasts disappeared these levels correspondingly fell, until on the twelfth day, when osteoclasts were practically absent, they returned to normal. Osteoblastic activity began

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17. Kramer, B.; Yuska, H., and Steiner, M. W.: Marble Bones: Chemical Analysis of Bone, Am. J. Dis. Child. **57**:1044-1057 (May) 1939.

18. Clifton, W. M.; Frank, A. A., and Freeman, S.: Osteopetrosis (Marble Bones), Am. J. Dis. Child. **56**:1020-1036 (Nov.) 1938.

19. Péhu, M.; Policard, A., and Dufourt, A.: L'ostéopétrose on maladie des os marmoréens, Presse méd. **39**:999-1003, 1931.

20. Selye, H.: On the Stimulation of New Bone Formation with Parathyroid Extract and Irradiated Ergosterol, Endocrinology **16**:547-557, 1932.

21. Pugsley, L. I., and Selye, H.: The Histological Changes in the Bone Responsible for the Action of Parathyroid Hormone on the Calcium Metabolism of the Rat, J. Physiol. **79**:113-117, 1933.

on the fourth day, in appreciable amount, and was constantly augmented thereafter. From this it would seem that as a result of parathyroid stimulation large numbers of osteoclasts are formed which phagocytose bone, thus shifting the calcium into the blood and the urine.

As to the actual role of the osteoclasts, much confusion exists,[22] for one school claims that the parathyroid hormone acts directly on the bones stimulating osteoclasis and the other claims that the presence of a large number of osteoclasts is not a specific hormonal reaction because it can be produced by procedures other than parathyroid stimulation. Thus, the latter group holds that the osteoclast phagocytoses the bony matrix only after decalcification has occurred. To us the former theory seems to be the likeliest, considering the evidence offered in osteopetrosis with administration of parathyroid injection producing little or no response; there is no hypercalcemia, nor is there any increased urinary excretion of calcium. None have attempted to explain this unusual phenomenon; however, when one considers the histologic picture, in which there is a definite paucity of osteoclasts[23] and, no doubt, an inability to form osteoclasts[24] in large quantity, it seems logical that parathyroid stimulation will not effect any mobilization of calcium.

In human beings suffering from osteopetrosis many estimations of blood elements have been made; few observers, however, have performed calcium and phosphorus metabolic studies. As a whole, calcium and phosphorus blood levels have been within normal limits except when associated with some other disease such as rickets. Flood[25] reported a serum calcium determination of 16.2 mg. per hundred cubic centimeters, which was the only elevated value observed. Several low levels of phosphorus in the serum have been seen in infants. However, in all, active or healing rickets was present, making difficult a decision as to the cause of such observations. It might also be emphasized at this time that it does not seem logical to compare the disease in adults, which presumably may be in the resting stage, with the disease in infants, in whom the disease process is active.

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22. Cantarow, A., and Trumper, M.: Clinical Biochemistry, ed. 3, Philadelphia, W. B. Saunders Company, 1945, p. 173.

23. *(a)* Pirie[8] *(b)* Jenkinson. Pfisterer, Latteier and Martin.[9] *(c)* Clifton, Frank and Freeman.[18] *(d)* Selye.[20] *(e)* Zwerg, H. G., and Laubmann, W.: Die Albers-Schönbergsche Marmorkrankheit, Ergebn. d. med. Strahlenforsch. **7**:95-136, 1936.

24. Krompecher, S.: Die Chondroklasie, normal und pathologisch, namentlich bei Marmorknochenkrankheit: Die Bedeutung und Funktion der Osteoklastenriesenzellen, Beitr. z. path. Anat. u. z. allg. Path. **104**:164-185, 1940.

25. Flood, R. G.: Calcium Metabolism in Marble Bone (Albers-Schönberg Disease), California & West. Med. **31**:203-204, 1929.

Concerning studies of calcium-phosphorus balance, it has been observed that the percentage of retention of these minerals is extremely high, as would be expected.

A summary of these studies appears in the table.

Summary of Reports of Calcium-Phosphorus Balance in the Literature

Author	Calcium Retention (Percentage)	Phosphorous Retention (Percentage)
Flood [25]	33	
McCune and Bradley[12]	65-83 (healing rickets)	37-47
Pincus, Gittleman and Kramer[26]	60 (healing rickets)	47
	59 (active rickets)	37
Clifton[18]	50	

Attempts to effect a negative calcium balance have been unsuccessful except those of Flood,[25] and he was on one occasion able to cause a loss of only 0.1098 Gm. of calcium by administering 25 units of parathyroid extract every thirty-six hours.

As a whole, excretion of calcium was almost entirely via the stool. In the cases of Pincus and his co-workers[26] and Flood,[25] 99 per cent of the calcium elimination was seen in the stool. This is extremely high, especially in view of the fact that there was no apparent reason. Pincus and his co-workers specifically denied the presence of any intestinal disorders. Flood observed no evidence of rickets. Of the patients of Pincus, 1 was suffering from active rickets, which would explain such a value (it is believed that in rickets and osteomalacia, although defective absorption plays an important role, the seat of trouble is defective intermediate calcium and phosphorus metabolism, so that normal ossification cannot take place, and as a result an increased amount of calcium is eliminated into the lower bowel); however, the disease in the other infant was definitely in the healing zone where one would expect a diminution in the amount of calcium in the stool, more being excreted in the urine.

Studies of phosphorus excretion were carried out by Pincus and his co-workers[26] and McCune and Bradley.[12] Their results coincide rather closely, in that in all 3 children studied about 80 per cent of the phosphorus excreted was seen in the urine. This is a characteristic of the healing stage in rickets, for which 2 of the infants were undergoing treatment. However, in a case such as that of Pincus and his co-workers, in which florid rickets existed, such an observation is unheard of. This led Pincus and his associates to postulate some increased parathyroid activity (a rise in urinary phosphorus being a cardinal laboratory characteristic of this disease).

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26. Pincus, J. B.; Gittleman, I. F., and Kramer, B.: Juvenile Osteopetrosis: Metabolic Studies in Two Cases and Further Observations on the Composition of the Bones in This Disease, Am. J. Dis. Child. **73**:458-472 (April) 1947.

That osteopetrosis is caused by increased parathyroid activity, no matter how small, seems rather doubtful; that there is some secondary stimulation of the parathyroid glands, however, seems probable.

When one considers the hereditary character of the disease, the generalized involvement with the attack on the hemopoietic system, the enlargement and fibrosis of the lymph nodes, the hepatosplenomegaly, the normal appearance of the parathyroid glands and the lack of laboratory evidence, such as hypercalcemia, elevated level of alkaline phosphatase in the serum and decided hypercalcuria, one can exonerate the parathyroid glands as the primary cause of the disease. However, such generalized bony changes and the observation of an elevated level of phosphorus excretion in the urine certainly point to some secondary parathyroid involvement.

Jongherr and Landauer[27] in 1938 reported an endemic outbreak of hypertrophic osteopathy in chickens. This spontaneous disease affected birds of both sexes and various breeds, usually between the ages of 4 and 6 weeks, causing thickening of the diaphysial sections of the leg and wing bones with the exception of the phalanges. These changes were usually associated with lesions of leukemic lymphomatosis. Histologic sections of the bones revealed a striking similarity to that seen in the human entity, being characterized by diffuse thickening of the substantia spongiosa and substantia corticalis accompanied with hypercalcification and narrowing of the medullary cavity. Microscopically there was noted lack of endochondral ossification, hypercalcification of nonlamellated interstitial connective tissue bone and marrow fibrosis. The trabeculae were hypertrophied and presented a mosaic structure with loss of normal architecture. Osteopetrosis gallinarum was suggested as a name for this condition, because of its resemblance to the condition in human beings. They divided the condition into three stages: initial, florid and resting. On further experimentation they observed that the disease could be reproduced by inoculating baby chicks with tissue from subjects with the disease in the florid stage only. This transmissible agent appeared to be present in blood, bone marrow and lymphomas. Sixty-one chicks were inoculated with the production of 6 subjects with gross lesions.

In similar work on chicks Burmester, Prickett and Belding,[28] using the RPL[1]-12 lymphoid tumor strain, obtained results closely paralleling those previously mentioned.

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27. Jongherr, E., and Landauer, W.: A Condition Resembling Osteopetrosis (Marble Bones) in the Common Fowl, Bulletin 222, Storrs Agricultural Experiment Station, 1938.

28. Burmester, B. R.; Prickett, C. O., and Belding, T. C.: A Filterable Virus Producing Lymphoid Tumors and Osteopetrosis in Chickens, Cancer Research 6:189-196, 1946.

They set up tests employing cell-free centrifuged suspensions of ground up lymphomas, the cell-rich sediment from them, as well as the blood cells and the plasma, which were filtered through a Sietz sterilizing filter pad. Inoculations of the 2 and the 3 day old chicks with these substances brought about the following results. The birds inoculated with viable cells died within a short time (two to ten days) of local and visceral tumor metastases. However, the chicks inoculated with the cell-free preparations, whether filtered or centrifuged, showed no pathologic condition until at least 10 weeks of age, at which time they began to exhibit signs of osteopetrosis, and by 6 months 41 per cent were affected with the malady. Fifty-six per cent of the birds presented microscopic visceral tumefactions; the liver was especially involved in these cases. A total of 80 birds were inoculated with cell-free preparations, and in 84 per cent there developed visceral, neural or bone involvement which was evident on gross examination. Of the 65 birds showing pathologic changes, 20 had osteopetrosis without gross evidence of other pathologic lesions. Twenty-nine had visceral tumors without osteopetrosis, and 16 had both. The average life span was 144 days.

Autopsy and histologic section revealed changes as described previously by Jongherr and Landauer.[27]

These observations are suggestive of a filterable substance, whether it be a virus in the true sense of the word or some other entity which may be the modus operandi in the disease in human beings. Further study and application to human beings must be made before any such tenet can be held with certainty.

Whatever is the cause of this disease—hereditary, viral or viroid, calcium-phosphorus inbalance or hormonal—the studies are intriguing and pregnant with potentialities. To our way of thinking the filterable substances offer the likeliest explanation.

DIFFERENTIAL DIAGNOSIS

With the fully developed syndrome of hepatosplenomegaly, anemia, multiple fractures, cranial nerve involvement, a carefully made and complete history, as well as a composite roentgenographic study of the skeleton, the diagnosis of osteopetrosis is not difficult.

Some of the uncommon conditions, as condensing osteitis of Sicard, eburnizing osteitis of Putti, ivory vertebra and meloreostosis, may present a problem, but, since these conditions are not generalized, a complete study of the skeletal system disposes of them. This will also exclude and differentiate osteopetrosis from leontiasis ossea, Paget's disease and osteitis fibrosa cystica.

Physiologic osteosclerosis of newborn infants and congenital syphilis have to be considered. The former is believed to represent a

physiologic storage of calcium and, like osteopetrosis, includes the entire osseous network. The increased density of the bones disappears in the course of the first few weeks of life, so that repeated roentgenologic studies will show decreased density. Congenital syphilis also shows osteosclerosis, but gives definite evidence of decided thickening of the periosteum, areas of destruction in the region of metaphysis and most characteristically does not attack the bones of the base of the skull. Serologic studies aid in establishing this diagnosis.

Interestingly enough, offspring of persons in any way associated with fluorine poisoning may show changes of the sclerotic type. But here, as in chronic fluorine poisoning, the architecture of bones remains unchanged and the adjacent soft tissues show osteophyte formation with calcification of intervertebral ligaments and periosseous deposits.

In the early stages of osteopetrosis it may be difficult to differentiate from lead poisoning, but if roentgenograms are taken of the feet and the skull, the differential diagnosis can probably be made, as the astragalus and sphenoid reveal evidence of marble bones early in the disease, whereas in lead poisoning there will be no evidence of changes in these bones. Chronic poisoning with lead and phosphorus show definite dense bands across the metaphysis in roentgenograms. Administration of vitamin D has also been reported to result in this phenomenon. In this metallic group of diseases, history, chemical analysis and microscopic examination of the blood establish a diagnosis.

The myelophthisic anemia in osteopetrosis does not differ notably from that in leukemia, but in this hematologic disease the bone changes are predominantly infiltrative and destructive. If there is involvement of the periosteum, the density is not so great and the extent of involvement is never so universal. The large number of nucleated red cells suggests familial erythroblastic anemia or a crisis in the course of familial hemolytic icterus. The roentgenogram of patients with familial erythroblastic anemia (Cooley's anemia) is characteristic, and there never have been reports of altered fragility in osteopetrosis, nor is its blood picture characterized by the presence of an abnormal number of microcytes.

Patients with cancerous metastasis or primary malignant conditions exhibit roentgenographically increased density, but only in isolated areas of the osseous system.

The most prominent symptom, namely, multiple fractures, may present some confusion with osteogenesis imperfecta, but roentgenograms in this disease show a lessened rather than increased density, although it also is generalized.

ROENTGENOLOGIC ASPECTS

Roentgenologically considered, osteopetrosis is a skeletal dystrophy in which increase in the density of the roentgenographic shadow cast by bone is the most characteristic feature. This increase is generalized and in typical cases is rather startling. The usual architectural features of normal bone, such as fine trabeculations of the substantia spongiosa, well proportioned cortices and marrow cavities, careful modeling or tubulation and sharply contrasting densities, are missing. The building of osteopetrotic bone appears to have been sublet to an amateurish contractor, who had an abundance of mineral salts available and used them with a lavish, if untrained, hand.

While the long bones, ribs and pelvis are the structures most commonly involved, the head, the spine and the bones of the hands and feet are frequently seen to manifest the changes of this disease.

The density of the shadows cast by these bones, as has been pointed out in the work of Kramer and his co-workers[17] and Clifton and his coworkers,[18] is due to the hypermineralization with normal chemical constituents. The lack of resorption of calcified cartilage, as is readily demonstrated histologically, further explains this increase in density in those bones preconceived in cartilage. Osteopetrotic changes, however, also occur in membranous bones, e.g., the bones of the calvarium, the ribs and the clavicles.

The roentgenographic picture varies with the severity of the disease. In the milder type of disease, first discovered when the patient has attained adult age, there may be little more than uniform increases in the density of the bones of the base of the skull, the spine and the pelvis. In the florid disease of early childhood, the entire skeleton may be involved and grossly disfigured.

While decidedly dense, osteopetrotic bone is not always uniformly so. Striking variations often occur in the shafts of the long bones, the carpal and tarsal bones and in the flaring portions of the iliac bones. At times translucent bands of decreased density of varying width are seen near the epiphysial plate and often extending well up the diaphysis. These are transverse strata of defective loose substantia spongiosa. They represent a period of growth in which excessive destruction of cartilaginous lattice has occurred and are somewhat of a paradox in osteopetrosis. Certainly some interruption or temporary cessation of the usual course of events in the laying down of osteopetrotic bone has occurred.

In other cases, there are longitudinal streakings and transverse striations of heavy density. These are probably only expressions of

arrested growth and, as has been demonstrated by the work of Harris,[29] may be met with in almost any systemic disease in which there is nutritional impairment for any length of time.

The faulty tubulation or modeling of the long bones, manifested most characteristically by heavy clublike expansion of the lower half of the shaft of the femur or upper half of the shaft of the humerus, is another interesting observation in osteopetrosis. That this type of deformity should occur is feasible, since it is well recognized from histiologic studies that there is a paucity of osteoclasis in osteopetrotic bone. It is the activity of these cells, with the aid of the restraining influence of an intact periosteum, that effects the nicely turned symmetric normal long bones.

The frequency of rickets seen in association with osteopetrosis is noteworthy. Several of the observations which we have just discussed, such as translucent bands, arrested growth lines and faulty tubulations, are just as common to rickets as they are to osteopetrosis.

The frequent association of osteopetrosis with osteomyelitis and delayed dentition are probably attributable to an impaired vascular supply, and consequently the nutritive requirements for normal development and maintenance of a healthy state are inadequate.

Fractures, likewise, are a common observation in the patient with osteopetrosis. These usually heal with the production of adequate, and at times, abundant, callus. However, delayed union is not unusual. Evidence of healed or healing fractures has been discovered with the patient having been unaware of their occurrence.

There are numerous references in the literature to the clublike thickening of the posterior clinoid process and narrowing of the sella turcica. It is claimed by some that these[12] are invariable observations and that one should hesitate to confirm a diagnosis of osteopetrosis in their absence. This, we believe, is a broad statement in light of the numerous types of sellae that we routinely see in the course of our daily work.

Ordinarily, the base of the skull is first and most decidedly affected by this disease. The bones of the calvarium, however, may also be involved and become so uniformly dense that no distinction can be made in the tables and the diploic portion. Obliteration and effacement of the mastoid cells and air spaces of the paranasal sinuses are fairly common. Narrowing of the various foramens of the skull, with compression of the corresponding emerging nerves, is not rare.

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29. Harris, H. A.: Bone Growth in Health and Disease: The Biological Principles Underlying the Clinical, Radiological and Histological Diagnosis of Perversions of Growth and Disease in the Skeleton, London, Oxford University Press, 1933.

PATHOLOGIC ASPECTS

The pathologic condition is limited to the hemopoietic system, the bones and the structures supplied by cranial nerves, as well as the cerebrum and the meninges.

The optic is the only cranial nerve that is affected with any frequency. However, deafness is common.

Hydrocephalus, thickening of the meninges and chronic subdural hematomas are frequently seen in children. Their production is explained on the theory that the narrowed cranial foramens increase the intracranial venous presssure, which may lead to bleeding with formation of chronic subdural hematoma or which will elevate the cerebrospinal fluid pressure, either of these eventuating in the formation of hydrocephalus.[12]

The liver, spleen and lymph nodes frequently show hypertrophy, in spite of which hematopoiesis is depressed, the enlargement being due in greater part to excessive fibrosis. Furthermore, the degree of anemia seems to parallel the size of these organs. There is no correlation between the roentgenographic appearance of bone and the anemia, for there are cases on record with complete obliteration of the marrow cavity, seen roentgenographically, with an essentially normal blood picture.

The peripheral blood has no characteristic features. The erythrocyte usually shows no changes except in size and volume, and these are not constant. Terminally, there may be hypoplastic anemia. Occasionally immature red cells may be seen, mostly normocytes. Platelets as a rule are not diminished. The leukocyte count may be normal or reduced. Infants, being more prone to leukocytosis than adults, may show young cells, mostly of the myeloid type.[12]

The bones offer the most interesting pathologic changes. Grossly, they appear white and brittle. Pirie,[3] in studying the resistance offered to a surgical drill by marble bone and a piece of chalk, expressed the belief that the latter cut with much more difficulty. Many surgeons, however, in working with these bones, insist that they are harder than normal. It is debatable, therefore, whether the frequency of fracture is due to the softness or to the loss of internal architectural elasticity.

Characteristically, the bones are thickened and encroach on the marrow cavity to the extent that it may be but a pinpoint. Also, the total circumference of the bones may be enlarged. This is especially seen in the clublike thickening of the upper third of the humerus and the lower end of the femur. On cross section, the bone may have a homogeneous dense appearance, with loss of differentiation between the substantia compacta and the substantia spongiosa. This is especially seen at the metaphysis. The marrow cavity and marrow spaces are naturally diminished, and what remain show extreme fibrosis, with loss of hemopoietic tissue similar to that of the other blood-forming organs previously mentioned.

HISTOLOGIC ASPECTS

Instead of the widely fenestrated delicate cartilaginous and later bony trabeculation, forming the primary spongy type of bone, one sees a predominantly solid calcified cartilaginous matrix in which numerous small irregular open spaces exist. Pirie[3] stated that these spaces comprise less than 25 per cent of the total structure. They are filled entirely or in part by amorphous primitive bony plaques.

The cause for this is revealed, in the work of Krompecher,[24] who stated that the cartilage cells, which normally swell and become rather large, remain small, thus leaving a large amount of hyaline matrix and small cellular spaces.

As is known, primitive mesenchymal and vascular connective tissue derived from the embryonic marrow cavity migrates into the provisional zone of ossification, burrowing paths through the calcified cartilaginous bars, and gains entrance to the large cavities left by the necrotic cartilage cells. One can easily see, then, that it is much more difficult for primitive marrow to gain entrance to this thick calcified hyaline structure than to the delicate honeycomb of normal cartilage; also, where penetration has occurred, the spaces are so small that, instead of the usual three or four layers of osteoblasts arranging themselves around a central large cavity, only one or two layers are possible and the central cavity is crowded, so that there is little chance for hemopoietic tissue to develop, especially the large giant cells or osteoclasts, which are uniformly reported to be conspicuously diminished in number.[30]

It is evident, then, that true bone formation is impossible, and, as a result, one sees broad areas of calcified cartilage, some of which contain within them true bone and similarly wide expanses of fibrous tissue containing centrally islands of bone, both apparently due to metaplasia.[30]

Many authors have reported an increased amount of osteoid;[31] the significance of this is unknown. Whether it is related to a vitamin deficiency or rickets has not been established. Clinically, rickets has been reported in combination with this disease, and the persistence of insulae of calcified hyaline cartilage in the metaphyses common to rickets has been seen.[18]

The marrow cavity and marrow spaces show fibrosis of varying degrees. This is one of the pathognomonic signs of the disease and is a constant observation.

30. (*a*) Pirie.[3] (*b*) Jenkinson, Pfisterer, Latteier and Martin.[9] (*c*) Krampecher.[24] (*d*) Zwerg and Laubmann.[25e] (*e*) Kijkstra, O. H.: L'ostéogénèse dans la maladie des os marmoréens, Ann. d'anat. path. **12**:131-141, 1935.

31. Pirie.[3] Jenkinson, Pfisterer, Latteier and Martin.[9] Clifton, Frank and Freeman.[18] Herscher, H., and Stein, J. J.: Osteopetrosis Associated with Hodgkin's Disease: Review of the Literature and Report of a Case, Am. J. Roentgenol. **43**:74-80, 1940.

Though this theory holds for the intracartilaginous development of bone, it certainly does not explain why the flat bones, developed within a membrane, are also affected. One must postulate then that, besides the disturbance in cartilage resorption, there is also an inability of true bone to form and assume normal structure. Instead one sees the heavy overgrowth of amorphous bony tissue previously described, blotting out diploe and marrow spaces in the flat bones.

PROGNOSIS AND TREATMENT

In the infant the outlook for life is generally poor, with death resulting from extreme inanition and intercurrent infection. Those who do survive usually have the stigmas of blindness, deafness, hydrocephalus, anemia and multiple fractures. In the adult, except for anemia and multiple fractures, the prognosis is generally favorable. Osteomyelitis is a serious complication. The treatment is ineffective. Several attempts have been made to mobilize calcium, without success.

SUMMARY

A case of osteopetrosis is presented, with complete laboratory and roentgenographic examination.

The causation is reviewed, with special attention to the possibility of a viroid origin, as demonstrated in birds.

Special attention is paid to the role of the cartilaginous precursor of bone in the development of this disease.

ASSOCIATION OF HEPATIC INSUFFICIENCY WITH CHRONIC ULCERATIVE COLITIS

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THE OCCURRENCE of disease of the liver in association with chronic idiopathic ulcerative colitis has received little emphasis. Pylephlebitic abscess is occasionally listed as an uncommon, but fatal, complication of ulcerative colitis[1] but nonsuppurative parenchymal hepatic disease is rarely mentioned. However, as early as 1899 Lister[2] reported a case of diffuse ulcerative colitis associated with a secondary acute interstitial hepatitis characterized by a diffuse cellular infiltration in the liver and the presence of an abundance of "fat globules." It is of interest to note that even before the separation of "simple ulcerative colitis" from the dysenteries by Wilks and Moxon,[3] Thomas[4] reported a fatal case of ulceration of the colon in which the rapidly fatal termination was felt to be due to a pathologic process in the liver. The liver was described as being enlarged to twice normal size, much softened and in an advanced stage of fatty degeneration. Logan[5] reported the autopsy findings in 13 cases of ulcerative colitis and found 1 instance of definite portal cirrhosis and 1 instance of "panhepatitis." In 9 instances the liver showed fatty changes and in 2 cases the liver was essentially normal except for the presence of cloudy swelling and edema. Cain and others[6] pointed out several years later that in the

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1. Bargen, J. A.: The Modern Management of Colitis, edited by M. Fishbein, New York, Doubleday, Doran & Company, Inc., 1934.

2. Lister, T. D.: A Specimen of Diffuse Ulcerative Colitis with Secondary Acute Diffuse Hepatitis, Tr. Path. Soc. London **50**:130, 1899.

3. Wilks, S., and Moxon, W.: Lectures on Pathological Anatomy, ed. 2, Philadelphia, Lindsay and Blakiston, 1875, p. 408.

4. Thomas, C. H.: Ulceration of the Colon with a Much Enlarged Liver, Tr. Path. Soc. Philadelphia **4**:87, 1874.

5. Logan, A. H.: Chronic Ulcerative Colitis: A Review of One Hundred and Seventeen Cases, in Collected Papers of the Mayo Clinic, edited by M. H. Mellish, Philadelphia, W. B. Saunders Company, 1918, vol. 10, p. 186.

slowly fatal cases of ulcerative colitis the liver is the site of a progressive fatty hepatitis. It was felt that the prognosis paralleled the state of the liver and that death occurred when the liver had undergone complete functional derangement. Other investigators[7] recognized the occurrence of parenchymal changes in patients with ulcerative colitis coming to necropsy, and it was suggested that the severe colitis was a secondary manifestation of underlying hepatic disease. Likewise, other authors[8] have emphasized the importance of changes in the liver in the course of chronic ulcerative colitis. Degenerative fatty changes have been particularly pointed out[8a] but a toxic infectious hepatitis has also been described,[8b] and since this type of change did not occur in every case of ulcerative colitis, a special clinical form of "rectocolitis with hepatic insufficiency" was postulated.[8]

In this country only two recent reports[9] have mentioned the importance of liver disease in ulcerative colitis. Comfort and associates[9a] described 4 cases with evidence of hepatic insufficiency. In 3 cases the colitis preceded the development of the hepatic insufficiency, but in the fourth case the hepatic insufficiency apparently occurred first. More recently Tumen and others[9b] reported 5 cases of hepatic cirrhosis occurring as a complication of ulcerative colitis. These 5 instances of cirrhosis occurred among a total of 151 cases of ulcerative colitis. In 4 cases the diagnosis of cirrhosis was established by peritoneoscopy. It was pointed out that there was clinical evidence of cirrhosis in 4 cases, but that in the fifth case there were no clinical signs to suggest such a diagnosis. For this reason it was suggested that the routine use of liver function tests in all cases of chronic ulcerative colitis would possibly uncover a much greater incidence of hepatic injury in this disease.

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6. (*a*) Cain, A., and Oury, P.: Les colites et les recto-colites ulcéreuses, Rev. crit. de path. et de thérap. **2**:707 and 813, 1931. (*b*) Bensaude, R.; Cain, A., and Massot, H.: Les lesions de la recto-colite ulcereuse aigue, Arch. d. mal. de l'app. digestif **22**:127, 1932.

7. Popovici, J. D.: L'Insuffisance hépatique et la côlite ulcéreuse grave, Gaz. med. de France (supp. gastro-enterol.), 1933, p. 6. Saccone, R., and Repetto, H. D.: La función hepática en las colitis ulcerosas, Actas Cong. nac. med. Rosario **5** (pt. 4)°:39, 1934; Arch. argent. de enferm. d. ap. digest. y de la nutricion **10**:179, 1934-1935.

8. (*a*) Cain, A., and Cattan, R.: Le role de l'hépatite dégénérative graisseuse dans l'évolution et le pronostic des recto-colites suppurées, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:673, 1937. (*b*) Caroli, J.; Busson, A., and Girard, P.: Contribution anatomoclinique à l'étude de l'atteinte hépatique au cours des côlites ulcéreuses graves, Arch. d. mal. de l'app. digestif **27**:762, 1937.

9. (*a*) Comfort, M. W.; Bargen, J. A., and Morlock, C. G.: The Association of Chronic Ulcerative Colitis (Colitis Gravis) with Hepatic Insufficiency, M. Clin. North America **22**:1089, 1938. (*b*) Tumen, H. J.; Monaghan, J. F., and Jobb, E.: Hepatic Cirrhosis as a Complication of Chronic Ulcerative Colitis, Ann. Int. Med. **26**:542, 1946.

In view of the lack of statistical data both on the incidence and the importance of nonsuppurative hepatic insufficiency in chronic ulcerative colitis, a study was undertaken to elucidate these points. The data dealt with included 70 cases of nonfatal and 17 cases of fatal ulcerative colitis in which necropsy was performed. All patients had been admitted to the University Hospital during the last five years, and the basis for the selection of nonfatal cases for inclusion in this study was that one or more tests of liver function had been carried out. The necropsied cases were studied whether such tests had been carried out or not. In this study of a total of 87 cases a total of one hundred and twenty-nine separate tests of liver function had been made as follows: sixty-three of serum protein, twenty-seven of prothrombin time, twenty-seven brom-

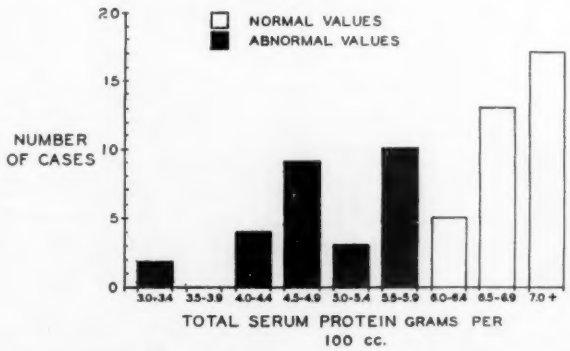

Fig. 1.—Total serum protein in cases of chronic idiopathic ulcerative colitis.

sulfalein tests and twelve cephalin cholesterol flocculation tests. In 21 cases two or more different tests of liver function had been carried out. In the 17 fatal cases the complete autopsy findings were studied. In 4 cases a diagnosis of cirrhosis was possible, two by autopsy and two by clinical data.

STUDIES OF THE FUNCTION OF THE LIVER

Serum Proteins.—Serum proteins were determined in 63 cases. The distribution of the results for total serum proteins is shown in figure 1. Values of 6 Gm. per hundred cubic centimeters or higher were considered within the normal range. It will be noted that of 63 cases, 28 demonstrated abnormally low total serum proteins. Although it is generally accepted that the level of the total serum proteins may reflect the functional state of the liver, one must be cautious in applying this interpretation in all instances, particularly in chronic ulcerative colitis

in which other factors may be operative in causing a reduction in this level. The most obvious other factor to be considered in ulcerative colitis is the nutritional status of the patient. For that reason an attempt was made to correlate the level of total serum protein with the nutritional state. This is indicated in table I in which loss of weight (employed as

TABLE 1.—*Relationship Between Loss of Weight and Total Serum Proteins in 63 Cases of Chronic Ulcerative Colitis*

Number of Patients	Loss of Weight (Pounds)	Average Total Serum Proteins (Gm. per 100 Cc.)
1	0 – 5	6.7
3	6 – 10	6.2
4	11 – 15	6.4
9	16 – 20	6.4
18	21 – 30	5.7
17	31 – 40	6.7
11	41 plus	5.7

a general index of nutritional status) was compared to serum protein level. It will be noted that there is no such correlation. For example, in those 17 instances in which the loss of weight was between 31 and 40 pounds (14 and 18 Kg.) the average total serum level was well within normal limits. The data at least suggest that the 28 instances of abnor-

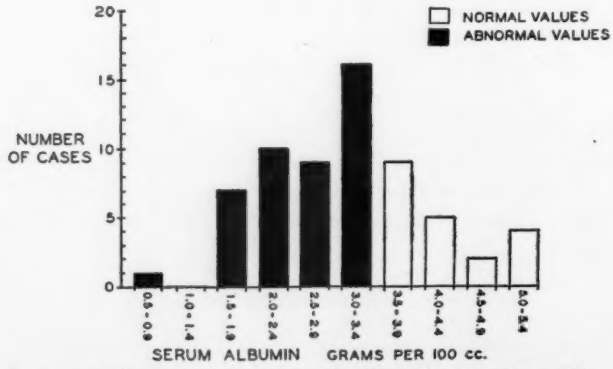

Fig. 2.—Serum albumin in cases of chronic idiopathic ulcerative colitis.

mally low total serum proteins are probably a reflection of hepatic insufficiency rather than nutritional deficiency.

In this connection it is well to point out that a loss of weight is a measure of caloric deficiency and not necessarily a measure of the possible deficiency of other essential nutrient factors. Although it is

true that deficiency of essential nutrients is more likely to occur where there is loss of weight, on the other hand, the qualitative aspects of the diet of those persons with no loss of weight and low total serum proteins require close evaluation before one can be certain that the low serum protein is entirely on the basis of hepatic insufficiency.

The level of the serum albumin fraction which is generally considered a more accurate measure of hepatic function than that of total serum protein is indicated in figure 2. If one considers values of 3 Gm. per hundred cubic centimeters or higher as within the normal range, it will be observed that in 27 of the 63 cases there is an abnormally low value. In no instance was there evidence of renal damage and as in the case of total serum proteins there was no correlation between the degree of loss of weight and the level of serum albumin. Hence, it appears at least

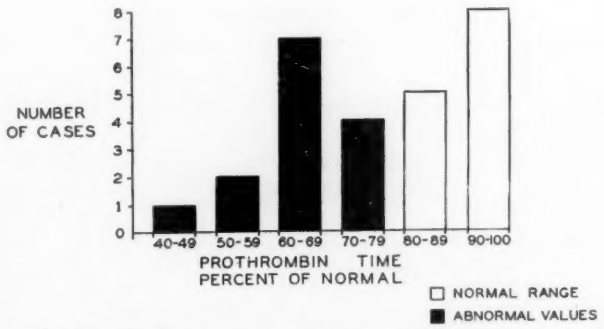

Fig. 3.—Prothrombin time in cases of chronic idiopathic ulcerative colitis.

suggestive that as reflected by the level of serum albumin, 43 per cent of our cases of chronic ulcerative colitis gave evidence of hepatic insufficiency.

Prothrombin Time.—The occurrence of prolonged prothrombin time has been frequently observed in chronic ulcerative colitis[10]. Thus, Page and Bercovitz[10d] found in frequent determinations of the prothrombin time in 25 cases of chronic ulcerative colitis that 28.5 per cent showed a constant hypoprothrombinemia, 61.9 per cent fluctuated between normal and abnormal and only 9.5 per cent were constantly normal.

10. (*a*) Stewart, J. D., and Rourke, G. M.: Prothrombin and Vitamin K Therapy, New England J. Med. **221**:403, 1939. (*b*) Mackie, T. T.: Vitamin K Deficiency in the Absence of Jaundice, New York State J. Med. **50**:987, 1940. (*c*) Butt, H. R., and Snell, A. M.: Vitamin K, Philadelphia, W. B. Saunders Company, 1941. (*d*) Page, R. C., and Bercovitz, Z.: Prothrombin and Fibrinogen Studies in Chronic Ulcerative Colitis, Am. J. Digest. Dis. **9**:419, 1942.

In our cases prothrombin time was determined in 27 cases. The levels for all cases expressed as per cent of normal prothrombin time are shown in figure 3. We accepted values of 80 per cent of normal time or more as being normal. Under such circumstances, 14 cases (51 per

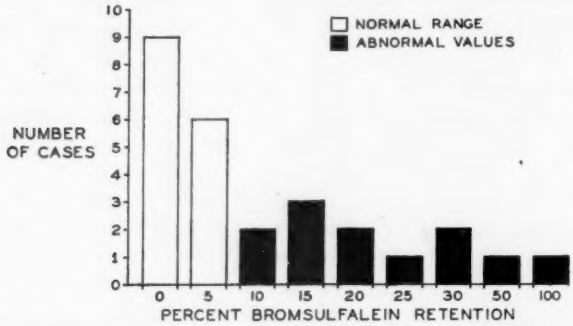

Fig. 4.—Results of bromsulfalein test in cases of chronic idiopathic ulcerative colitis.

cent) revealed abnormally low levels. The low level of the prothrombin in itself could not necessarily be accepted as an indication of hepatic insufficiency, but could be readily interpreted, as previously suggested,[10b] as a manifestation of deficient intake or absorption of vitamin K. How-

TABLE 2.—*Results of Cephalin Cholesterol Flocculation Test in 12 Cases of Chronic Ulcerative Colitis*

Case	Duration (Months)	Loss of Weight (pounds)	Cephalin Flocculation	
			24 Hours	48 Hours
1	24	0	++	++++
2	24	0	0	0
3	48	0	++	++++
4	18	10	0	++
5	24	12	0	+
6	1	15	0	0
7	15	20	0	0
8	4	22	+	++++
9	12	27	0	0
10	5	31	0	0
11	5	35	++	++++
12	24	40	++	++++

ever, our data are more significant as an indicator of hepatic insufficiency in view of the fact that all prothrombin values indicated were determined after administration of adequate daily supplementary vitamin K, generally supplied parenterally.

Bromsulfalein Test.—The bromsulfalein dye retention test was carried out in 27 cases. In all instances 5 mg. of dye per kilogram of body weight was administered intravenously and the degree of dye retention determined at the end of forty-five minutes. Retention of 10 per cent or more of the dye was considered abnormal. Employing this criterion, 12 (44 per cent) of our 27 cases revealed evidence of hepatic insufficiency (fig. 4). In view of the fact that it has been suggested that any degree of retention of dye is indicative of hepatic disease, it may be of significance that in 6 additional cases there was a retention of 5 per cent of the dye at the end of forty-five minutes.

TABLE 3.—*Comparison of Various Tests of Liver Function in 21 Cases of Chronic Idiopathic Ulcerative Colitis**

Case	B.S.P.	Cephalin Cholesterol	Prothrombin Time	Total Serum Protein
1	+	+	+	+
2	−	−	+	+
3	+	+	−	+
4	+	+	−	−
5	+	+	−	+
6	−	−	−	
7	−		−	−
8	−		−	−
9		+	+	+
10			−	+
11			+	−
12			+	−
13			−	−
14		−	−	
15	−		−	
16			+	+
17	+			+
18			+	+
19	+	+		
20	−			−
21	−			+

*Normal —; abnormal +.

Cephalin-Cholesterol Flocculation Test.—Table 2 indicates the results obtained from the use of this test in 12 cases of chronic ulcerative colitis. Following the suggestion of Mateer[11] the test was considered to be positive, that is indicative of active parenchymal disease of the liver, only if there was at least a two plus reaction at the end of forty-eight hours. Six (50 per cent) of the 12 cases of ulcerative colitis revealed damage of the liver as reflected by this test. An attempt was made to determine whether there was any relationship between either the duration of the ulcerative colitis or the degree of malnutrition as indicated by the loss of weight and the presence of hepatic insufficiency as reflected by this

11. Mateer, J. G.; Baltz, J. I.; Marion, D. F., and MacMillan, J. M.: Liver Function Test, J. A. M. A. **121**:723 (March 6) 1943.

test. As indicated in table 2 there is no relationship with either of these two factors. For example, there are positive and negative results of tests in cases of short duration (compare cases 10 and 11) and also in cases of long duration (compare cases 5 and 12). Likewise, there are positive and negative reactions both where there is no loss of weight (cases 1 and 2) and where there is marked loss (cases 10 and 12).

Comparison of Various Tests of Function of the Liver.—In view of the fact that the four function tests employed were often carried out on different patients, there is rather good agreement in the results as far as they indicated the percentage of patients with chronic ulcerative colitis who have hepatic insufficiency. Thus, in the tests employed abnormality was revealed as follows: serum albumin, 43 per cent; prothrombin time, 51 per cent; bromsulfalein, 44 per cent, and cephalin-cholesterol flocculation, 50 per cent. However, a more accurate comparison of the results of these tests can be obtained by evaluating them in those instances in which two or more tests were carried out in the same patient at the same time. This was true in 21 cases. Using the criteria already described for abnormal tests, we compared in table 3 all tests carried out in the same patient. It will be noted that in all instances in which both the bromsulfalein and the cephalin-cholesterol flocculation tests were carried out there is agreement as to the presence or absence of hepatic insufficiency. The prothrombin time agrees with the results of the bromsulfalein and cephalin-cholesterol flocculation test in 4 instances and is at variance with these tests in 4 instances. Likewise, the total serum proteins are in agreement with the dye and flocculation tests in 3 instances but at variance in 4 instances. The prothrombin time and total serum proteins are generally in agreement with each other as tests in evaluating hepatic function. It thus appears that the bromsulfalein and flocculation tests best reflect the functional capacity of the liver in ulcerative colitis, with the level of the total serum proteins and the prothrombin time being of less value.

Definite Instances of Hepatic Cirrhosis.—As previously indicated, 10 definite instances of hepatic cirrhosis associated with chronic ulcerative colitis have been reported in the literature.[12] In our material 4 cases revealed definite evidence of hepatic cirrhosis in association with chronic ulcerative colitis. Because such instances have been reported so uncommonly, a brief summary of each case is presented.

Case 1.—W. B. (case 17, table 6), a 20 year old woman, was admitted to the University Hospital on March 8, 1943, with the history of persistent mucous and bloody diarrhea of ten to fifteen stools daily since March 1938. This diarrhea had persisted in spite of various types of oral and parenteral therapy. It had been unassociated with fever, anorexia, nausea or loss of weight. Abdominal cramping had been present intermittently since the onset of diarrhea. For one year prior

12. Logan.[5] Comfort and others.[9a] Tumen and others.[9b]

to admission there had been mild tenderness in the right lower quadrant. There was no history of infectious jaundice or of the ingestion of hepatotoxic drugs. The past history was not significant. On admission physical examination revealed a well nourished woman (weight, 138 pounds [62.6 Kg.], height 64 inches [162.56 cm.]) who did not appear ill. Aside from generalized abdominal tenderness and hepatic enlargement (3 cm. below the right costal margin) the examination gave negative results. There was sigmoidoscopic and roentgen evidence of chronic ulcerative colitis. Cultures of the stools did not reveal pathogenic organisms, and the examinations for parasites all gave negative results. There was a moderate hypochromic anemia (hemoglobin 9.8 Gm. per hundred cubic centimeters). The patient was given succinylsulfathiazole, a high protein, soft fiber diet, iron and supplementary vitamins. She improved promptly, and by the time of discharge (April 26, 1943) the stools were one to two daily and formed. Her weight was 141 pounds (64 Kg.). After discharge she did well until October 1943. At this time the stools increased to five to six daily, and there was undue fatigue. This continued, but was associated with a gain in weight to 150 pounds (68 Kg.). She was readmitted on Feb. 21, 1944. Physical examination now revealed a pale, chronically ill woman.

TABLE 4.—*Summary of Results of Liver Function Tests in Case 1*

Date	Prothrombin*	Cephalin† Flocculation	Blood Bilirubin (mg %)	Hippuric Acid‡	Galactose Tolerance#	Serum Proteins			
						Total	Alb.	Glob.	A/G
2–24–44						8.9	4.3	4.6	0.9
3–25–44	65								
4– 4–44	57	++++	2.0	0.55					
4–10–44	66		2.0			7.8	2.6	5.5	0.5
4–28–44	65		3.8						
5– 2–44	58		7.0						
5– 8–44	72								
5–18–44	61				3.69				
5–24–44	57		2.5			8.1	3.4	4.7	0.8
5–31–44	50								
6–12–44	62	++++	6.0	0.70	3.1	6.1	1.9	4.2	0.5
6–29–44	55		6.0						
7–13–44	46								

*Per cent of normal. †Forty-eight hour reading. ‡Intravenous test gave normal results: 1 Gm. or mor excreted in one hour. #Oral test gave normal results: 3 Gm or less excreted in five hours.

There were ascites and generalized peripheral edema. The therapeutic program of the first admission was reinstated. There was slight improvement with a decrease of the stools to three to four daily. Icterus was first observed on March 25, 1944. After this her condition deteriorated rapidly and in spite of intensive therapy, including a protective liver diet, the patient became worse and died on July 19, 1944. The results of the tests of liver function which were carried out are summarized in table 4. It should be noted that the prothrombin time was obtained in spite of massive amounts of parenterally administered vitamin K. Autopsy revealed chronic ulcerative colitis and toxic parenchymatous hepatitis in both subacute and healed stages.

Comment: This is a clearcut case of severe hepatic disease in association with chronic ulcerative colitis. The evidence appeared to indicate clearly that the hepatic disease had its onset subsequent to the colitis and seemed to become manifest and progressive simultaneously with an exacerbation of the colonic disease.

CASE 2.—E. Q. (case 16, table 6), a 24 year old man, was admitted to the University Hospital on Aug. 22, 1944, with the complaints of diarrhea and weakness. Diarrhea had begun in March 1939, following acute infection of the upper

respiratory tract. Stools had varied in number from five to ten daily and had frequently contained small amounts of fresh blood. Various sulfonamide compounds and a bland diet had had little influence on the diarrhea. The weight had varied from 126 to 135 pounds (57.2 to 61.2 Kg.), but during the last few weeks prior to admission it had increased to 145 pounds (65.8 Kg.). His appetite had remained excellent. There had been two recent short febrile episodes with a temperature up to 101 F. Until two months prior to admission there had been no abdominal pain, but at that time a dull ache developed in the right flank and persisted until admission. Associated with the pain the patient had noted a gradual increase in the size of the abdomen. During the same period there was a questionable history of the presence of jaundice. The stools had varied from yellow to dark brown and the urine had occasionally been dark. Aside from the occurrence of nonseasonal hay fever since childhood the past history was irrelevant. There was no history of the ingestion of hepatotoxic drugs or any history suggestive of infectious hepatitis. Physical examination on admission revealed a malnourished man. There was no fever. The skin was pasty and pale, but not icteric. The nasal mucosa was boggy and edematous. There were definite ascites and slight peripheral edema. Roentgen studies of the gastrointestinal tract on Aug. 24, 1944, were reported on as follows: "Probable widespread segmental inflammatory disease of the small bowel, colon and rectum; nonfunctioning gallbladder; hepatomegaly; ascites." Results of laboratory studies are given in table 5.

TABLE 5.—*Results of Laboratory Studies in Case 2*

Date	Hemoglobin (Gm/100 Cc.)	Blood Bilirubin	Prothrombin (% of Normal)	Serum Proteins Total	Albumin	Globulin
8/22/44	2.6	0.9	40	7.2		
8/29/44	5.9	17.5	40	6.4	2.2	4.2
9/ 6/44	8.9	20.0				

Daily small transfusions were immediately started, and he was given a high protein soft fiber diet, large amounts of vitamin K parenterally and succinylsulfathiazole. From the onset the stools were tarry and liquid. Jaundice was first observed on the fourth day in the hospital. His condition deteriorated, and it was not possible to maintain his hemoglobin because of continuous loss of blood by rectum. For these reasons, an ileostomy was performed on the seventh day in the hospital. The patient tolerated the operation well and gradually improved. However, the ascites gradually reaccumulated and on the nineteenth day in the hospital he had a massive hematemesis and died. The autopsy revealed extensive chronic ulcerative colitis, chronic acute yellow atrophy of the liver (fig. 5) and ruptured esophageal varices.

Comment: This, also, is a clearcut case of severe disease of the liver associated with ulcerative colitis. The loss of blood that terminated the picture was incorrectly presumed to be due to bleeding from the colon but actually was due to bleeding from esophageal varices consequent on the hepatic disease. In this case, again, the hepatic disease apparently had its onset subsequent to the ulcerative colitis.

CASE 3.—B. W., a 21 year old woman, had been well until December 1943, at which time, after an acute infection of the upper respiratory tract, she began to have chronic fatigue and severe chronic constipation. Enemas and cathartics were resorted to for relief, but shortly thereafter there was the onset of diarrhea characterized by the passage of five to ten bloody stools daily. This was accompanied by severe abdominal cramping. She was hospitalized in her local hospital and

improved under medical therapy, with the stools diminishing to one to two daily. In May 1944 there was a recurrence of all her original symptoms. Her past history revealed that in the winter of 1941 the patient had "catarrhal jaundice," with jaundice persisting for three months. There was also an episode of jaundice in January 1943, which lasted about two weeks. She was first admitted to the University Hospital on July 25, 1944. Examination at this time showed a chronically ill but well nourished woman (weight 144 pounds [65.3 Kg.], height 62 inches [157.48 cm.]. Her temperature was 99.2 F. There was tenderness in the right lower abdominal quadrant, but the physical examination otherwise gave normal results. The hemoglobin value was 6.2 Gm. per hundred cubic centimeters. Roentgenograms revealed evidence of widespread inflammatory disease of the small bowel and colon. The sigmoidoscopic picture was characteristic of chronic ulcerative colitis. Results of cultures of the stools were all within normal limits.

TABLE 6.—*Summary of Results of Liver Function Tests in Case 3*

Date	B.S.P.*	Cephalin Flocculation		Serum Proteins				Prothrombin†	Hippuric Acid‡
		24	48	Total	Alb.	Glob.	A/G		
1- 6-44				6.8	3.6	3.2	1.1		
7- 25-44									
1- 9-45	100			8.0	4.0	4.0	1.0		0.8
1-16-45	90								
5-14-45	25								0.9
11-15-45	90			7.3	3.3	4.0	0.82		
12- 1-45		++++	++++						
5-14-46	40	++++	++++						
8- 8-46				8.8	4.2	4.6	0.92		
8-15-46		++++	++++	8.2	4.0	4.2	0.95		
9-13-46				9.8	4.6	5.2	0.99		
10-12-46				9.0	4.2	4.8	0.87	80	
3-10-47	100	++++	++++	9.2	4.6	4.6	1.0		
5- 8-47		++	++++						

*5.0 mg. per kilogram readings at forty-five minutes. †Per cent of normal. ‡Intravenous test normal: 1. Gm. or more excreted in one hour.

Chemotherapy, rest in bed and high protein, low fiber diet resulted in prompt symptomatic relief. Since the original admission, this patient has been seen at frequent intervals. Up to the present time there have been two severe recurrences, but during the last year the patient had not had diarrhea, worked daily and her weight was 170 pounds (77.1 Kg.). In January 1945 the liver was first found to be palpable about 5 cm. below the right costal margin. It was hard in consistency but not nodular. There was definite splenomegaly. There had been three episodes of edema of the face and ankles. Since January 1946 the patient had been given a high protein diet, choline and phthalylsulfathiazole. For the last year she had done well, having a definite remission of colitis. The results of the tests of liver function carried out in this patient are summarized in table 6.

Comment: In contrast to the previous 2 cases, in this instance there is definite evidence that the serious disease of the liver apparently had its onset prior to the

ulcerative colitis. The history of "catarrhal jaundice" in 1941, with a possible recurrence of jaundice in January 1943, is highly suggestive that in this instance we were dealing with chronic hepatitis or hepatic cirrhosis occurring as the end result of an infectious hepatitis. One can only speculate as to the influence of the severe colitis either in adding further damage to an already diseased liver or in influencing the progression of the chronic hepatitis.

CASE 4.—F. M., a 46 year old man, was well until March 1942. At that time severe headaches, dyspnea and cardiac failure developed. Severe hypertension was discovered by his family physician. Symptoms of cardiac failure persisted, and for this reason the patient was first admitted to the University Hospital on July 8, 1943. At this time examination revealed, in addition to other signs of cardiac failure, marked ascites and hepatomegaly. The patient responded well to digitalis, diuretic drugs and rest in bed. He was discharged on Aug. 15, 1943. He remained well until June 1944, when cardiac failure recurred. This persisted in a chronic form until he was readmitted to the University Hospital on Jan. 25, 1945. At this time there were marked cardiomegaly, hepatomegaly and splenomegaly, as well as ascites. Treatment with digitalis and diuretic drugs resulted in cardiac compensation, and because of persistent hypertension, a bilateral supradiaphragmatic resection of the splanchnic nerve was carried out. Postoperatively the blood pressure became normal and remained at this level until time of discharge on April 25, 1944.

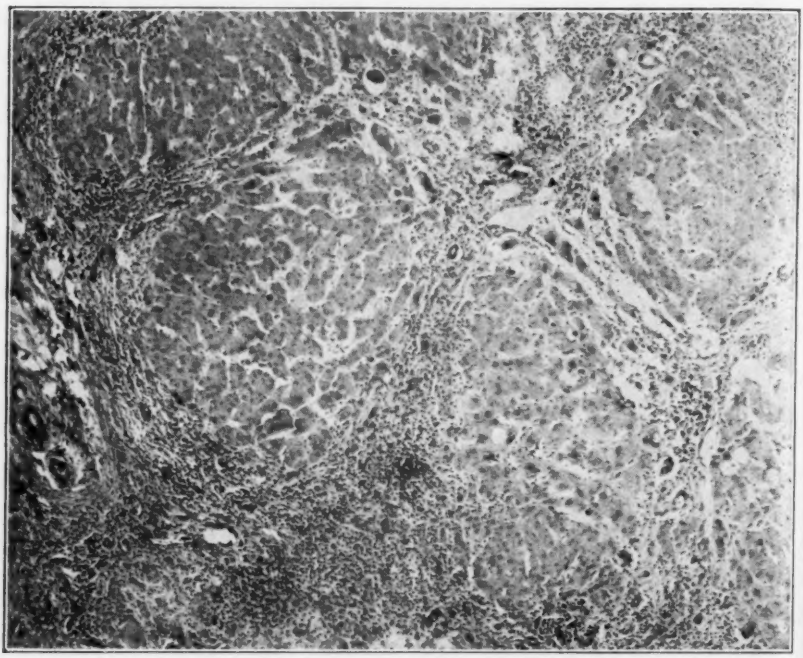

Fig. 5.—Low power view of liver in a case of chronic ulcerative colitis (E. I., case 16, table 6). This was interpreted as "chronic acute yellow atrophy."

The patient had no further cardiac difficulties. In November 1945 he first noted gross blood in his stools. Shortly thereafter he began to have gradual increase in his stools, finally passing fifteen to twenty bloody, liquid stools daily. Associated with this there was generalized lower abdominal discomfort and marked anorexia. There was a 35 pound (15.9 Kg.) loss of weight during the two months prior to his admission to the University Hospital on March 9, 1946. Physical examination at this time revealed a normal blood pressure, cardiomegaly and tenderness in both flanks. The liver and spleen were palpable. There was no ascites or peripheral edema. There was sigmoidoscopic and roentgen evidence of chronic ulcerative colitis. The hemoglobin value was 11 Gm. per hundred cubic centimeters. The patient's course in the hospital was stormy. The temperature rose to 101.4 F. daily. The stools continued up to fifteen daily. There was persistent anorexia, and weight decreased approximately 5 more pounds (2.3 Kg.). However, at no time was there evidence of cardiac failure. After six months of hospitalization the patient was improved sufficiently to be transferred to his local hospital for further care. The results of the liver function tests carried out on this patient are given in table 7.

TABLE 7.—*Results of Liver Function Tests in Case 4*

Date	Bromsulfalein	Cephalin Flocculation Test	Prothrombin Time	Serum Proteins		
				Total	Albumin	Globulin
2/ 1/45	50%			7.6	4.8	2.8
2/ 7/45	15					
3/25/46	15	4				
6/19/46				7.8	3.4	4.4
7/16/46	25		100			
9/ 5/46				6.9	3.5	3.4

Comment: In this case there was definite ulcerative colitis and definite evidence of severe hepatic disease. However, there was evidence of liver insufficiency (bromsulfalein 50 per cent on Feb. 1, 1945) prior to the onset of the ulcerative colitis. At that time it was felt to be associated with his frequent and chronic episodes of cardiac failure. However, at the time of the occurrence of his ulcerative colitis there was no clinical evidence of cardiac failure. One is thus forced to speculate that in this case there was probably preexisting damage of the liver ("cardiac cirrhosis") and that the ulcerative colitis was a factor only in that it added further damage or caused an exacerbation or progression of the liver insufficiency.

Autopsy Findings in Chronic Ulcerative Colitis.—Autopsy findings in 17 fatal cases (including cases W. B. and E. Q.) of chronic ulcerative colitis were studied. Special emphasis was placed on the histologic changes in the liver. The essential data in these cases are tabulated in table 8. It will be noted that there were 10 female and 7 male patients in this series. The age varied from 2½ to 40 years. Symptoms had been present for one month to six years. In all cases there had been an appreciable loss of weight. Histologically there were definite abnormali-

ties of the liver parenchyma in all but 1 case (case 1). In 2 cases[13] there were definite changes characteristic of cirrhosis. In all other cases there was either fatty infiltration or degenerative fatty infiltration or both. Degenerative fatty infiltration is widely accepted as evidence of the functional impairment of the hepatic cells to handle lipids normally. It is considered early evidence of hepatic insufficiency. If we exclude case 1 and all other cases in which only simple fatty infiltration was present, we

TABLE 8.—*Summary of Findings in 17 Autopsied Cases of Chronic Idiopathic Ulcerative Colitis*

Case	Sex	Age	Duration of Symptoms (Months)	Loss of Weight (Pounds)	Hepatic Pathologic Process
1	F	31	60	35	Acute exacerbation chronic passive congestion; no lipoidosis
2	F	34	2	30	Marked fatty infiltration
3	M	17	4	17	Fatty infiltration; cloudy swelling; simple atrophy
4	M	2½	1	?	Marked degenerative fatty infiltration; cloudy swelling
5	M	37	9	27	Patchy fatty infiltration; acute exacerbation chronic passive congestion
6	M	39	36	85	Marked lipoidosis; simple atrophy; cloudy swelling; acute passive congestion
7	F	17	7	16	Marked fatty and degenerative fatty infiltration; cloudy swelling
8	F	24	12	54	Extreme fatty infiltration and slight degenerative fatty infiltration
9	M	15	37	21	Marked fatty infiltration; cloudy swelling; simple atrophy
10	M	40	30	43	Peripheral degenerative fatty infiltration
11	F	17	3	14	Fatty infiltration peripheral portion of lobules; cloudy swelling
12	F	37	1½	31	Advanced fatty infiltration; focal excessive vacuolar change in parenchyma
13	F	29	1½	?	Marked fatty infiltration; slight degenerative fatty infiltration; moderate lymphocytic infiltration in triads
14	F	27	5	?	Marked degenerative fatty infiltration; increase in lymphocytes in trinities
15	F	17	4	26	Very marked fatty infiltration; increased wandering cells in portal canal
16	M	24	60	10	Chronic acute yellow atrophy
17	F	20	72	10	Toxic parenchymatous hepatitis in subacute and healed stages

find that 11 of our 17 cases show definite evidence of damage to the liver. It will be recalled that these figures correspond closely with those of Logan.[5]

COMMENT

The occurrence of hepatic insufficiency in approximately 50 per cent of our cases of ulcerative colitis and the occasional occurrence of frank

13. Page and Bercovitz.[10d] Mateer and others.[11]

cirrhosis does not appear to be a fortuitous association. In an occasional ease (e.g., cases 3 and 4) in which the onset of the cirrhosis occurred prior to that of ulcerative colitis the hepatic insuffciency probably cannot be related fundamentally to the intestinal disease. However, in the vast majority of our cases the evidence seems to indicate that the hepatic insufficiency is fundamentally and etiologically related to the occurrence of ulcerative colitis. The following facts support this point of view: 1. The hepatic insufficiency developed after the onset of the colitis. 2. Hepatic insufficiency of such severity as to lead to cirrhosis is at least twice as common in males as in females.[14] Ulcerative colitis is equally common in both sexes.[15] 3. Cirrhosis is most common above the age of 40,[14] while ulcerative colitis is most common below that age.[15]

Studies of the hepatic histology at necropsy indicate in both our series and that of Logan[5] that fatty changes in the liver are common in ulcerative colitis. This fatty change, while it may vary in severity and degree, appears to be the basis for the hepatic insufficiency that is reflected in diminished function of the liver as detected by clinical and laboratory means. Once fatty infiltration is present, the possibility that more severe insufficiency and finally frank hepatic cirrhosis may develop has been demonstrated conclusively, both in animals[16] and in man.[17] The only point to be considered further is the origin of the fatty changes in the liver in ulcerative colitis. We believe there are two main factors: the severe malnutrition and the toxemia that are present in the disease. Both of these conditions occurring in many diseases are known to produce fatty infiltration of the liver.[18] The situation in tuberculosis, particularly, when there is severe malnutrition and toxemia, is entirely analogous to ulcerative colitis.[19]

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14. Ratnoff, O. D., and Patek, A. J., Jr.: The Natural History of Cirrhosis of the Liver, Medicine **21**:207, 1942.

15. Willard, S. H.; Pessel, J. F.; Hundley, J. W., and Bockus, H. L.: Prognosis of Ulcerative Colitis, J. A. M. A. **111**:2078 (Dec. 3) 1938.

16. Chaikoff, I. L.; Cannon, C. L., and Biskind, G. R.: Fatty Infiltration and Cirrhosis of the Liver in the Depancreatized Dog Maintained with Insulin, Am. J. Path. **14**:101, 1938.

17. Connor, C. L.: The Etiology and Pathogenesis of Alcoholic Cirrhosis of the Liver, J. A. M. A. **112**:387 (Feb. 4) 1939.

18. Mottram, V. H.: Fatty Infiltration of Liver in Hunger, J. Physiol. **38**:281, 1909. Ralli, E. P.; Paley, H., and Rubin, S. H.: Liver Lipids and Their Distribution in Disease: Analysis of Sixty Human Livers, J. Clin. Investigation **20**:413, 1941.

19. Jones, J. M., and Peck, W. M.: Incidence of Fatty Liver in Tuberculosis with Special Reference to Tuberculous Enteritis, Arch. Int. Med. **74**:371 (Nov.) 1944. Hurst, A.; Maier, H. M., and Lough, S. A.: Studies of Hepatic Function in Pulmonary Tuberculosis, Am. J. M. Sc. **214**:431, 1947.

Our concept of the development of hepatic insufficiency in ulcerative colitis is that as a result of malnutrition, toxemia or both, fatty changes occur in the liver. These fatty changes may be of sufficient degree to give rise to hepatic insufficiency of such slight degree that it can be detected only by tests of liver function, or it may progress to definite cirrhosis. Because the onset of the liver insufficiency is that of a fatty change, early in its course, it is reversible and is probably amenable to the influence of lipotropic substances. In our data we attempted to correlate loss of weight as a measure of malnutrition with the occurrence of liver insufficiency. No correlation could be detected. However, since loss of weight is no accurate measure of nutritional deficiency, this cannot be considered a serious objection to our concept of the development of hepatic insufficiency. Moderate or no loss of weight may occur in the presence of specific nutritional deficiencies (protein, choline, and so forth), and the converse may likewise, be true.

SUMMARY AND CONCLUSIONS

Study of hepatic function in patients with chronic idiopathic ulcerative colitis by means of the bromsulfalein test, cephalin-cholesterol flocculation test, prothrombin time and serum protein revealed the presence of hepatic insufficiency in approximately 50 per cent of the 70 cases investigated.

The bromsulfalein and cephalin-cholesterol flocculation tests appeared the most satisfactory indicators of hepatic insufficiency.

In 11 of 17 cases of chronic ulcerative colitis studied post mortem, there was histologic evidence of a hepatic pathologic process. Degenerative fatty infiltration was most common, but definite cirrhosis was present in 2 instances.

Four cases of cirrhosis of the liver associated with chronic ulcerative colitis are reported. In 2 instances the cirrhosis had its onset prior to the colitis and was probably not related etiologically to the latter. In the other 2 cases the cirrhosis had its onset after the colitis.

Evidence is presented to indicate that hepatic insufficiency in association with ulcerative colitis probably has its origin in fatty changes in the liver that occur as a consequence of severe malnutrition or toxemia or both.

STUDY OF TREMOR IN SOLDIERS

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THE CLINICAL study of tremors has been the subject of a great deal of investigation. Tremors occur in a wide variety of conditions. Most observations, however, have been confined to disease states such as Parkinson's disease and multiple sclerosis. In such conditions as thyrotoxicosis, alcoholism and anxiety states a tremor of the outstretched fingers is considered an important, if not a cardinal, clinical sign. That a tremor can also occur in normal persons has long been known but generally overlooked. "My flesh trembleth for fear of the Lord," a quotation taken from the Bible,[1] illustrates the antiquity of this observation.

In the course of a study of palmar sweating among soldiers at an army general hospital, it was found that soldiers with an excessive palmar sweat response frequently exhibited pronounced tremors. A study was therefore undertaken to investigate and correlate these phenomena. To study the sweat response, the technic of Silverman and Powell[2] was used. In this technic a sweat pattern of the finger tips is portrayed on chemically treated paper. Prints are obtained which vary in intensity according to the amount of sweating. A response was considered intense when a black, blotchy stain was produced (fig. 1). To record the tremors, a modification of an apparatus described by Morris[3] was used. An ordinary 6 inch (15 cm.) loud-speaker was enclosed, except for its opening, in a rigid wooden cabinet. The opening of the speaker was sealed over with a tight rubber diaphragm, being thus converted into an air-tight chamber (fig. 2). The wooden cabinet was of sufficient length and width to provide a comfortable base for the upper extremity, and the hand was permitted to rest on the rubber diaphragm. With this arrangement the vibrations of the fingers were transmitted through the loud-speaker and converted into electrical energy. The latter was finally picked up and recorded with an ordinary electrocardiograph machine (General Electric and Sanborn models were both used). Each patient was seated comfortably in a quiet room, free from distracting influences. With experience, it was learned that better

1. Psalms 119:120.

2. Silverman, J. J., and Powell, V. E.: Studies on Palmar Sweating: I. A Technique for the Study of Palmar Sweating, Am. J. M. Sc. **208**:297, 1944.

3. Morris, A. A., Jr.: An Apparatus to be Used in Recording Tremors, Arch. Neurol. & Psychiat. **49**:123 (Jan.) 1943.

results were obtained when the hand was placed in contact with the diaphragm in such a way that the thenar, hypothenar and tips of the distal phalanges made contact with its surface (fig. 3).

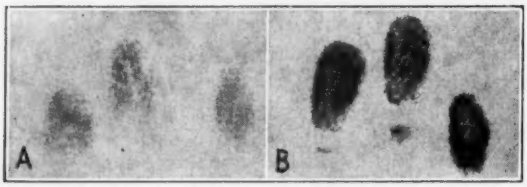

Fig. 1.—Classification of sweat pattern. *A* shows mild response and *B* intense response.

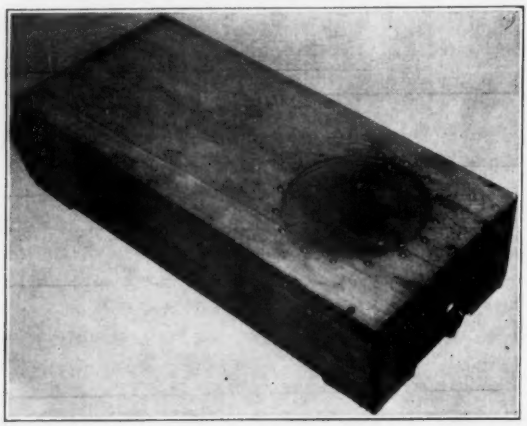

Fig. 2.—Loud-speaker unit, enclosed in cabinet, for transmitting tremors (United States Army Signal Corps photograph).

Fig. 3.—Patient in position for recording of a tremor. The loud-speaker unit is connected with an electrocardiographic machine (United States Army Signal Corps photograph).

The tremor apparatus was found to be extremely sensitive in reproducing tremors, and a system had to be devised to standardize the results. Officers with no clinically demonstrable tremors of the fingers of the outstretched hand, confirmed by two or more competent observers, were used for calibration. Tremor records were then made for these officers, and the amplification was so adjusted that the finished record barely demonstrated oscillations of less than 1 mm. (fig. 4). The apparatus was kept at this amplification throughout the study. With this standardization it was found that clinically pronounced tremors always measured at least 5 or more millimeters on the graph and frequently measured

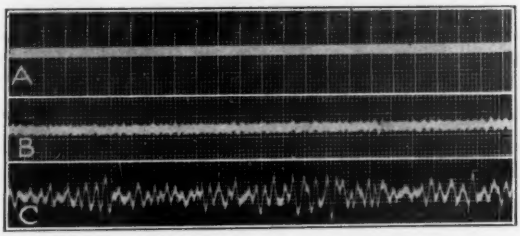

Fig. 4.—Classification of tremor. *A*, record of a tracing taken without a patient; *B*, example of a tremor of low amplitude; *C*, example of a tremor of pronounced amplitude.

more than 10 mm. (figs. 5 and 6). In classifying a tremor, measurements were taken from the peak to the trough of each wave. All tremor waves were measured and the average amplitude determined. Records measuring from 1 to 5 mm. in amplitude were considered equivocal and excluded from the classification of pronounced tremor. At frequent intervals the apparatus was checked and adjusted for accuracy.

The records were obtained by trained army personnel. The tremor of one hand was recorded, and the other hand was used for the study of the palmar sweat response. No set plan was followed, but usually the tremor record was obtained first. In many cases the tremor record and the sweat pattern were obtained simultaneously. To insure accuracy, the tests were frequently repeated on the same patient. It should be emphasized that the test situation was more or less similar for all patients

In an army hospital, and even before reaching a hospital, soldiers are subjected to all kinds of tests, and they were in most instances conditioned to a study of this nature.

FINDINGS

The tremor and sweat patterns in a total of 321 persons, divided into three groups, were studied. The findings in all groups are summarized in the table.

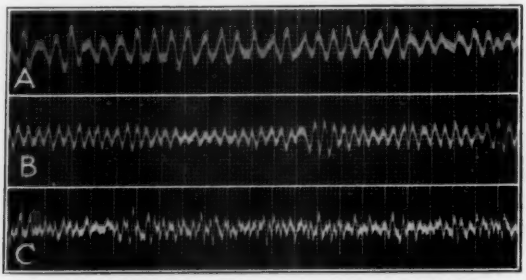

Fig. 5.—Examples of variations in tremor rates. In *A* the rate is 7 per second, in *B* 12 per second and in *C* 21 per second.

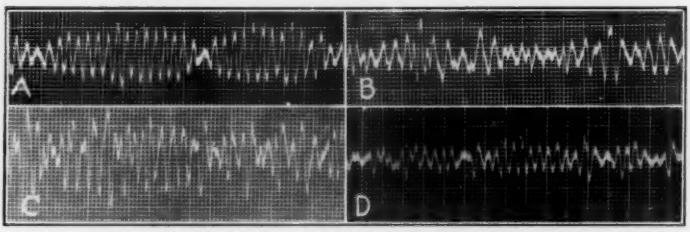

Fig. 6.—Illustration of the wide variety of tremor patterns. *A*, from a patient with a history of alcoholism and anxiety; *B*, from a patient in a severe anxiety state; *C*, from a patient with conversion hysteria; *D*, from a medical officer who consciously tried to produce a tremor.

The first group consisted of 174 soldiers who were in the process of undergoing basic military training at an Army Infantry Replacement Center. All these soldiers were recruits, and the average age was 19 years. In this group 30 (17.2 per cent) were found to have a pronounced tremor, and 25 (14.4 per cent) demonstrated an excessive palmar sweat response. There were 6 soldiers (3.5 per cent) who demonstrated a pronounced tremor and an excessive palmar sweat response at the same time.

The second group consisted of 111 patients who were under observation in the hospital for complaints referable chiefly to the cardiovascular system. These patients were carefully examined, and all kinds of tests, such as electrocardiographic and roentgenologic studies, blood counts and urinalyses, were made. In addition, consultations with other specialists, including psychiatrists, were obtained. No patient in this group was found to have organic disease as the basis of his complaints, and the majority were finally discharged from the hospital with a diagnosis of neurocirculatory asthenia. Anxiety features predominated in these patients. In this group there were 67 (60.4 per cent) who showed a pronounced tremor and 33 (29.7 per cent) who showed an excessive palmar sweat response. In 25 (22.5 per cent) excessive sweating and a pronounced tremor were present.

The third group consisted of 36 normal persons. In a study of this nature it is difficult to classify so-called controls, for normalcy is, after all, a relative term. Nevertheless, it was decided to use medical officers, nurses and laboratory technicians of a high rating as controls. All members of this group were considered healthy and, as far as could be determined, were emotionally stable. In this control group there were only 2 (5.6 per cent) with a pronounced tremor, and not one demonstrated a pronounced tremor and excessive palmar sweating at the same time. On the other hand, there were 6 in this group with an excessive palmar sweat response.

Throughout this study there was no characteristic tremor peculiar to each group. In all groups studied the pattern was essentially irregular, and because of this irregularity it was sometimes difficult to assign an exact frequency to a particular tremor. The tremor rates varied from 7 to 21 per second, and the average was 14.2 per second (fig. 5).

COMMENT

The significance of the sweating of the palms has been taken up elsewhere.[4] It has been shown that sweating of the palms is unique and differs from general body sweating on anatomic and physiologic grounds. The palmar sweat response is one of the important indexes of the emotions. It is increased during emotional excitement.

The physiologic interpretation of tremors is complex and beyond the scope of this paper.[5] It is not sufficiently appreciated, however, that

4. Silverman, J. J., and Powell, V. E.: (*a*) Studies on Palmar Sweating: II. The Significance of Palmar Sweating, Am. J. M. Sc. **208**:298, 1944. (*b*) Studies on Palmar Sweating: III. Palmar Sweating in an Army General Hospital, Psychosom. Med. **6**:243, 1944.

5. Morris, A. A., Jr.: The Nature of Tremors, North Carolina M. J. **5**:15, 1944.

tremor, like palmar sweating, is a normal phenomenon and takes place continuously. Eshner[6] in 1897 was the first to demonstrate clearly the occurrence of a tremor in normal persons. Using a modified sphygmograph, Eshner[6] showed objectively that a tremor existed in every one of his 100 normally tested subjects. In emotional crises, such as in fright and rage, Cannon[7] has shown that the sympathetic system is overactive and tends to discharge en masse. Clinically, the striking changes are similar to those produced by adrenalemia: tachycardia, dilated pupils, pallor and tremor. During excitement, excessive palmar sweating also takes place, and although this is a cholinergic mechanism it has been shown that the system is also stimulated during such stages.[8]

A relationship of cortical activity to variations in tremors has long been known.[9] The usual cited tremor rate is 10 per second,[10] which

Analysis of the Incidence of Tremors of High Amplitude and Excessive Palmar Sweating in 111 Patients and in a Group of 174 Trainees and 36 Controls

	Excessive Sweat		Pronounced Tremor		Tremor and Sweat	
	No.	%	No.	%	No.	%
Patients (111)	33	29.7	67	60.4	25	22.5
Trainees (174)	25	14.4	30	17.2	6	3.5
Controls (36)	6	16.7	2	5.6	0	0.0

incidentally corresponds to the major potential rhythm of the electroencephalogram seen in studies of the region of the cortex of the brain anterior to the central fissure.[11] That the cortex is not the sole controlling influence in tremors is illustrated by their appearance in such conditions as Parkinson's disease and multiple sclerosis, in which changes can be demonstrated in other areas of the brain.

Tremors vary widely in rate, amplitude and pattern. Attempts to classify tremors on the basis of these variations, however, have met with little clinical success. A tremor has been likened to auricular fibrillation, i.e., an irregular irregularity. The lack of standardization of the technics in recording tremors has further complicated the problem of classification and accounts for many of the conflicting reports

6. Eshner, A. A.: A Graphic Study of Tremor, J. Exper. Med. **2**:301, 1897.

7. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage: An Account of Recent Researches into the Function of Emotional Excitement, New York, D. Appleton & Company, 1929.

8. Gellhorn, E.: Autonomic Regulations: Their Significance for Physiology, Psychology and Neuropsychiatry, New York, Interscience Publishers, Inc., 1943.

9. Fulton, J F.: Physiology of the Nervous System, New York, Oxford University Press, 1938.

10. Young, J. C.: A Study of Tremor in Normal Subjects, J. Exper. Psychol. **16**:644, 1933.

11. Jasper, H. H., and Andrews, H. L.: Brain Potentials and Voluntary Muscle Activity in Man, J. Neurophysiol. **1**:87, 1938.

appearing in the literature.[12] Using a sensitive oscillograph, Travis and Hunter[13] recorded a tremor frequency close to 200 per second. Figure 5 demonstrates the wide variation of rate and pattern of tremors found in our study, and, as shown, rates varying from 7 to 21 per second

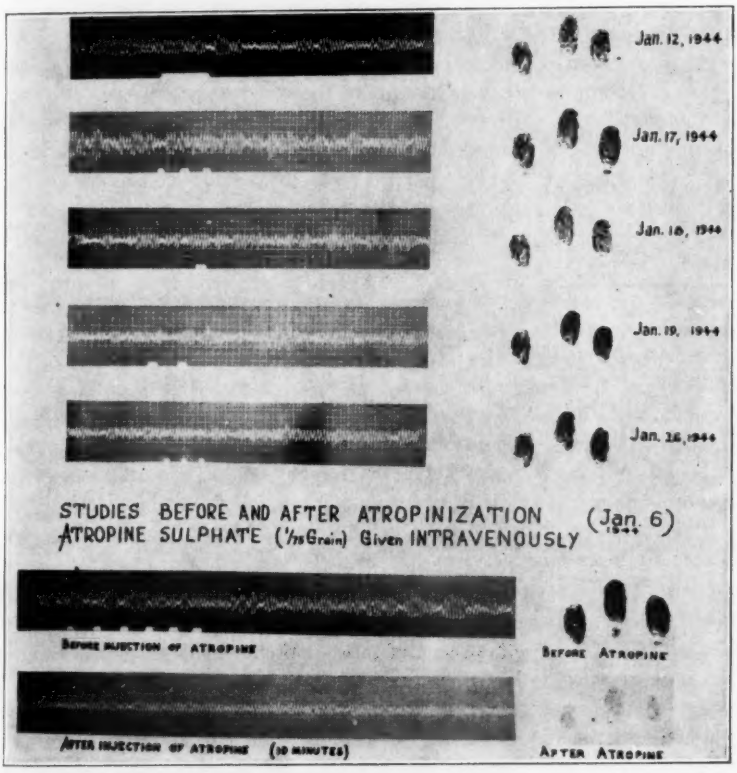

Fig. 7.—Study of tremor and palmar sweat response in a soldier suffering from severe neurocirculatory asthenia. Note the diminution in amplitude after the administration of atropine.

were observed The amplitude of a tremor, on the other hand, would seem to have more clinical significance.[14] As Young[10] pointed out, when

12. Sollenberger, R. T.: Tremor During Postural Contraction, J. Exper. Psychol. **21**:579, 1937.

13. Travis, L. E., and Hunter, T. A.: Tremor Frequencies, J. Gen. Psychol. **5**:255, 1931.

14. French, J. W.: A Comparison of Finger Tremor with the Galvanic Skin Reflex and Pulse, J. Exper. Psychol. **34**:494, 1944. Graham, J. D.: Static Tremor in Anxiety States, J. Neurol. & Psychiat. **8**:57, 1945.

a tremor is modified as a result of emotional influences, the variation will be largely with respect to the amplitude and hardly at all with respect to the rate. In the course of our studies an interesting experiment was conducted which bears out this observation. A 29 year old corporal with an established diagnosis of severe neurocirculatory asthenia was studied daily for tremor and sweat records. It was known that belladonna had a quieting effect on the patient, and one morning atropine sulfate (0.87 mg.) was administered intravenously. Sample records are shown in figure 7. It was found that throughout the study of this patient the rate of the tremor (11 per second) was remarkably constant; the amplitude, on the other hand, showed definite variations. After the administration of atropine sulfate, the amplitude of the tremor, as well as the sweat response, was strikingly reduced. In many records of other patients, it was surprising to find how constant the rate was regardless of the state of tension.

In our study of various groups of army personnel, the relative incidence of tremors of large amplitude was shown. A pronounced type of tremor was found in all groups, and, confirming a well known clinical impression, the highest percentage of these tremors was found among soldiers with anxiety features. Almost two thirds of the patients with the syndrome of so-called neurocirculatory asthenia demonstrated a pronounced tremor. A similar type of tremor was also found among the recruits but not as frequently. In the control group, made up mostly of selected army personnel, a pronounced tremor, though demonstrable, was decidedly uncommon. It would seem therefore, in a general way, that a tremor of large amplitude offers some diagnostic information.

A study of the incidence of pronounced tremors associated with excessive palmar sweating in the same patient was definitely more revealing. It was found, for example, that close to one fourth of the soldiers suffering from neurocirculatory asthenia showed both excessive palmar sweating and a significant tremor, whereas among the recruits less than 4 per cent were in this category and among the controls there was not one who demonstrated both an excessive palmar sweat pattern and a significant tremor. It would seem from this study, therefore, that the association of excessive palmar sweating and notable tremors in the same person takes on more diagnostic significance than the evaluation of each finding separately.

Except for certain neurologic disorders, a tremor by itself has little diagnostic significance. As stated previously, a tremor is a normal phenomenon, easily modified by outside influences. The tremor of alcoholism cannot be distinguished from the tremor of fear or cold. There is no characteristic tremor in hyperthyroidism.[15] The distinction between a fine and a gross tremor is merely one of amplitude; one easily

merges into the other, depending on the state of tension. Similarly, the distinction between a rapid and a slow tremor cannot always be made. In our experience, it was extremely difficult to predict, on clinical grounds, the rate of a tremor. Nevertheless, statements can still be found in textbooks[16] assigning a tremor of a certain rate to a specific disorder.

A tremor takes on significance only when it is correlated with other signs, particularly those related to the autonomic nervous system. Its association with excessive palmar sweating, for example, is a striking feature of an anxiety state. In our study, this combination was seen almost exclusively in patients suffering from neurocirculatory asthenia, a condition now considered to be part of an anxiety state with emphasis on the cardiovascular system.[17] This observation of excessive palmar sweating associated with tremors of large amplitude is not new and has been commented on as a feature of the neuroses met in wartime.[18] It is hazardous to establish a diagnosis on the basis of a tremor alone. A volitional or hysterical type of tremor may closely resemble an anxiety tremor (fig. 6), and a differential diagnosis may be difficult. In evaluating a tremor, it is important to examine the palms for sweating. A dry palm in an anxious patient is an anomaly.[4b]

SUMMARY

1. A tremor, like palmar sweating, is a normal physiologic process, easily modified by outside influences.

2. Tremors vary widely according to their rate, amplitude and pattern. Under emotional influences the variation is chiefly with respect to amplitude.

3. A tremor of high amplitude was demonstrated in widely selected groups of army personnel, but the highest incidence was found among emotionally disturbed soldiers.

4. An excessive palmar sweat response and a tremor of high amplitude were found to exist together in the same patient almost exclusively in the group suffering from anxiety features (neurocirculatory asthenia). This combination was not found in any of the normal persons.

5. A tremor takes on clinical significance only when it is correlated with other signs. In evaluating a tremor, it is important to examine the palms for sweating.

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15. Lazarus. S., and Bell, G. H.: Tremor in Hyperthyroidism, Glasgow M. J. **140**:77, 1943.

16. Wolf, W.: Endocrinology in Modern Practice, Philadelphia, W. B. Saunders Company, 1936.

17. Dunn, W. H.: Emotional Factors in Neuro-Circulatory Asthenia, Psychosom. Med. **4**:333, 1942.

18. Wood, P.: Etiology of Da Costa Syndrome, Brit. M. J. **1**:845, 1941. Grinker, R. R. and Spiegel, J. P.: War Neurosis, Philadelphia, The Blakiston Company, 1945.

PERNICIOUS ANEMIA IN THE TROPICAL NEGRO

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ACCORDING to most published data, pernicious anemia appears to have an uneven distribution in different parts of the world, being a disease chiefly of the temperate zone, more particularly North America, the British Isles and Northern Europe. Information concerning its incidence in the tropics is meager in the better known textbooks of medicine. In addition to this lack of knowledge, there are divergent opinions as to the role that race plays in the distribution of the disease, especially in relation to the frequency among Negroes.

From a review of the literature, the prevailing impression is gained that the incidence of the disease in Negroes is increased in proportion to the amount of intermixture with white persons. Cornell[1] quoted Longcope as saying that pernicious anemia seldom if ever occurs in full-blooded Negroes. Kracke[2] adhered to this same view and stated that after a careful watch for the disease at the Grady Hospital in Atlanta, Ga., for the past ten years he has not observed a case among a large number of Negroes admitted. However, Wintrobe[3] felt that the rareness of the occurrence of pernicious anemia in full-blooded Negroes has been overemphasized. He presented 33 cases involving Negroes among a total of 329 patients with the disease admitted to the Johns Hopkins Hospital between the years 1925 and 1940. At Peter Bent Brigham Hospital, Friedlander[4] reviewed 500 cases of the disease among a total of 80,145 persons admitted, of which 4,503 were Negroes. Only 3 Negroes with pernicious anemia, or 0.07 per cent of the total number admitted, were found. Kampmeier and Cameron[5] studied the number of patients with pernicious anemia admitted to the Louisiana State Charity Hospital during the decade 1926 to 1936. They reported 98 cases of the disease among the white persons and 14 among the Negroes.

From Gorgas and Colon hospitals, Panama Canal Health Department, Cristobal, Canal Zone.

1. Cornell, B. S.: Pernicious Anemia, Durham, N. C., Duke University Press, 1927.

2. Kracke, R. R.: Diseases of the Blood and Atlas of Hematology, ed. 2, Philadelphia, J. B. Lippincott Company, 1941.

3. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1943.

4. Friedlander, R. D.: Racial Factor in Pernicious Anemia, Am. J. M. Sc. **187**:634, 1934.

5. Kampmeier, R. H., and Cameron, P. B.: Pernicious Anemia in the Negro, Am. J. M. Sc. **192**:751, 1936.

The disease occurred seven times more frequently among the white patients since an equal number of white persons and Negroes were admitted. Schwartz and Gore[6] reviewed the literature up to 1943 and found 106 reported cases of pernicious anemia among Negroes. They studied 1,000 consecutive patients with this disease who entered Cook County Hospital in the interval from 1931 to 1942 and found 93 of them to be Negroes. The ratio of white persons to Negroes in their series was about 10 to 1.

Pernicious anemia is extremely uncommon among natives of tropical and oriental countries.[7] Strong[8] quoted from a report on anemias of the tropics made by Dr. De Langen and Dr. Lichenstein in Java in which they stated that they have never observed a case of pernicious anemia in a native. They also related that pernicious anemia does not occur among the Negro races in Africa, but occasionally it has been found in certain of the tribes in the neighborhood of Lake Tanganyika. Wills[9] has described a tropical macrocytic anemia in India which is almost indistinguishable from pernicious anemia both clinically and hematologically. Because of the multiplicity of complicating disorders she has been unable to classify this anemia more definitely.

The problem of determining what persons should be included under the term Negro is one of great magnitude. It was not possible to ascertain the presence or percentage of admixture of white and Negro blood with any degree of certainty, but we can state that the overwhelming majority of our patients were of Negro parentage and came from a native Negro habitat. In addition, we employed as our criteria a combination of the anthropologic[10] definition of the Negro and the commonly accepted clinical characteristics such as the dark brown to sooty black skin, flat broad nose, everted lips, woolly hair, prognathous jaws with large teeth, dark eyes and the typical negroid facies.

SELECTION OF CASES

The diagnostic criteria employed in the selection of cases were those which have been well established for the disease. Clinical recognition

6. Schwartz, S. O., and Gore, M.: Pernicious Anemia in Negroes, Arch. Int. Med. **72**:782 (Dec.) 1943.

7. Kracke.[2] Wintrobe.[3] Friedlander.[4]

8. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 7, Philadelphia, The Blakiston Company, 1945.

9. Wills, L., and Evans, B. D. F.: Tropical Macrocytic Anemia, Lancet **2**:416, 1938.

10. Encyclopaedia Britannica, ed. 14, New York, Encyclopaedia Britannica, Inc., 1929. Kroeber, A. L.: Anthropology, New York, Harcourt, Brace & Company, 1923. Haddon, A. C.: The Races of Man, New York, The Macmillan Company, 1925.

was based on symptoms referable to the anemia and to the gastrointestinal and neurologic systems, with 3 of the patients having varying degrees of subacute combined sclerosis. Achlorhydria following the injection of histamine was present in all cases except case 1, in which the diagnosis was made at necropsy. Examination of the blood revealed a macrocytic anemia, with an increased mean corpuscular volume and mean corpuscular hemoglobin content. Peripheral blood smears revealed anisocytosis and poikilocytosis. Leukopenia and thrombopenia were present in 3 cases. Three patients had elevated icteric indexes, which returned to normal after therapy. In 6 cases, including 2 at necropsy, the structure of the bone marrow was characteristic of pernicious anemia. The stools were normal, and in only 1 case were parasites found. The parasite was Trichuris trichiura. Roentgenograms of the upper gastrointestinal tract were made in 8 cases and found to be normal. The therapeutic test using parenterally administered liver was employed and was followed by reticulocytosis, rapid relief of symptoms and a rise in the red blood cell count (table).

REPORT OF CASES

CASE 1.—L. H., a 66 year old Jamaica-born Negro woman, was admitted to the hospital because of severe asthenia and dyspnea. Examination showed the patient to be malnourished and dehydrated and to appear gravely ill. The mucous membranes of the mouth were pale, and the tongue was heavily coated and dehydrated. The scleras appeared icteric. The hemoglobin content was 3.75 Gm. per hundred cubic centimeters, the red blood cell count 1,200,000 and the white blood count 7,800, with 57 per cent neutrophils and 43 per cent lymphocytes. A smear did not reveal malaria, and the peripheral blood smear revealed many nucleated red cells. The patient died in her sleep the evening of her admission to the hospital before any further studies could be made. Autopsy revealed considerable megaloblastic proliferation of the bone marrow, lemon yellow–colored fat and a moderate hemosiderosis of the internal organs. The cause of death was pernicious anemia.

CASE 2.—G. M., a 51 year old Barbadian-born Negro, was admitted to the hospital because of progressive dyspnea and paresthesias of the lower extremities of three months' duration. The latter became so severe that he was unable to walk unaided. The past history disclosed an untreated penile lesion. Examination revealed a senile, oriented, chronically ill man. An enlarged heart was present, with a systolic aortic blowing murmur. There was ataxia of both upper and lower extremities, with muscle weakness, a tabetic gait and positive reactions to the Rhomberg and the finger to nose tests. The pupils reacted well, and all deep tendon reflexes were absent. A hemogram revealed a hemoglobin content of 7.5 Gm. per hundred cubic centimeters, a red blood cell count of 2,350,000 and a white blood cell count of 5,200, with 62 per cent neutrophils, 2 per cent eosinophils and 36 per cent lymphocytes. The reticulocyte count was 0.7 per cent, and the volume index was 1.255. The peripheral blood smear did not reveal malaria or the sickling trait but did reveal anisocytosis and macrocytosis. The mean corpuscular

Data in 10 Cases of Pernicious Anemia

Case	Sex	Age	Place of Birth	Year of Admission	Blood Admixture*	Hemoglobin Content, Gm./100 Cc.		Red Blood Cells, Millions/Cu. Mm.		Reticulocytosis %		Hematocrit, Cc./100 Cc.		Mean Corpuscular Volume in Cubic Microns on Admission	Mean Corpuscular Hemoglobin in Micro-Micrograms on Admission	Bone Marrow	Roentgenograms of the Upper Gastro Intestinal Tract	Achlorhydria
						Admission	Discharge	Admission	Discharge	Admission	Maximum	Admission	Discharge					
1	F	66	Jamaica	1933	0	3.75	-------	1.2	-------	-------	-------	-------	-------	-------	-------	Diagnostic (necropsy)	-------	—
2	M	51	Barbados	1942	+	7.5	11.5	2.35	4.08	0.7	5.0	32	41	130	32.6	Not examined	Normal	+
3	M	41	St. Vincents	1943	+	5.4	10.5	2.2	4.0	1.1	8.6	24	40	100	26	Diagnostic	Normal	+
4	M	50	Barbados	1944	+	5.25	9	1.9	3.5	-------	7.6	-------	-------	-------	-------	Diagnostic (necropsy)	Normal	+
5	M	51	Barbados	1946	+	2.9	13	0.92	4.2	2.6	28	9.5	-------	103.2	31.5	Diagnostic	Normal	+
6	M	47	Colombia	1946	—	6.7	12.6	2.26	3.53	0.1	15.1	21	-------	93	29	Unsatisfactory examination	Normal	+
7	F	55	Jamaica	1947	—	5.6	12.6	1.35	4.47	0.1	37	15	-------	118	41	Not examined	Normal	+
8	M	55	Barbados	1947	+	6.5	14.8	1.99	4.23	0	7	17	37	90	34.2	Diagnostic	Normal	+
9	M	60	Panama	1947	+	5.6	13.2	1.26	3.82	0.5	16.6	13	-------	103	44	Not examined	Normal	+
10	M	70	Barbados	1947	+	3	9	1.02	3.0	1	35	11	-------	104	33	Diagnostic	Unsatisfactory	+

*The plus sign means that both parents were Negroes, the minus sign that one parent was 50 per cent Caucasian and the zero that no knowledge relating to the parents was obtained.

hemoglobin was 32.6 micromicrograms. Achlorhydria was present after the administration of histamine. The reaction of the blood to serologic tests was positive, but examination of the spinal fluid revealed it to be normal. Roentgenograms of the upper gastrointestinal tract were normal. Liver therapy was instituted, and eight days later a reticulocyte count of 5 per cent was noted. Neurologic consultation confirmed the original findings, and a diagnosis of subacute combined sclerosis was made. The hemoglobin content and the red blood cell count progressively increased to 11.5 Gm. and 4,080,000 cells respectively two months after treatment was started. The mean corpuscular volume was 97.3 cubic microns and the mean corpuscular hemoglobin 31.6 micromicrograms. Reevaluation by the neurologic department demonstrated a normal gait, with a return of the vibratory sensation. The patient felt clinically well and was discharged to the outpatient department for observation.

CASE 3.—I. S., a 41 year old St. Vincentian-born Negro, was admitted to the hospital because of a traumatic amputation of his left foot. The physical condition was normal except for the partial loss of the affected limb. A hemogram made on his admission revealed a hemoglobin content of 10.5 Gm. and 3,240,000 red blood cells. The white blood cell count was 9,450, with 78 per cent neutrophils, 2 per cent eosinophils and 20 per cent lymphocytes. His convalescence was benign except for an unexplained anemia which progressively developed five weeks after admission. The hemoglobin content dropped to 7.5 Gm. and the red blood cell count to 2,000,000. The white blood cell count was 3,250, with a normal differential count. Repeated analyses of the stools showed them to be normal. Examination revealed glossitis and a low grade fever, the temperature fluctuating to 99.6 F. The patient was given ferrous sulfate and vitamin therapy, which had no effect on the progression of the anemia. Eight weeks after admission examination revealed pronounced diminution of vibratory sensation in the right ankle. The hemoglobin value had fallen to 5.4 Gm. and the red blood cell count to 2,200,000. The reticulocyte count was 1.1 per cent, and the blood smear revealed anisocytosis and poikilocytosis. Gastric analysis revealed achlorhydria after the administration of histamine. The hematocrit value was 24. The mean corpuscular volume was 109 cubic microns, the mean corpuscular hemoglobin was 26 micromicrograms and the mean corpuscular hemoglobin concentration was 23 per cent. Liver therapy was instituted, and three days later the reticulocyte count was 8.1 per cent. Daily reticulocyte counts revealed a fluctuation from 8.1 per cent on the third day of therapy to 8.6 per cent on the eighth day. The reticulocytosis gradually declined so that twenty days after the institution of therapy the count was 0.6 per cent. The hemogram showed progressive improvement, and eighteen days after administration of liver was begun the hemoglobin content was 9.0 Gm. per hundred cubic centimeters and the red blood cell count 3,380,000. The patient felt much improved, and the tongue was no longer smooth. Six weeks after therapy was instituted, the vibratory sensation returned to normal. The hemoglobin content was 10.5 Gm. per hundred cubic centimeters and the red blood cell count 4,000,000. The reticulocyte count was 0.7 per cent and the hematocrit value 40. The mean corpuscular volume was 105.3 cubic microns, the mean corpuscular hemoglobin 31.6 micromicrograms and the mean corpuscular hemoglobin concentration 30 per cent. The patient was discharged to the outpatient department for follow-up and continued therapy. He has been subsequently admitted to the hospital twice, once for revision of the stump and the second time for an exacerbation of his anemia. The hemoglobin content was 4.0 Gm. per hundred cubic centimeters, the red blood cell count 1,450,000 and the hematocrit value 12.5. Sternal marrow puncture revealed a

picture compatible with pernicious anemia. A series of gastrointestinal roentgenograms was normal. The patient responded well to transfusions and to liver therapy. At the time of his discharge to the clinic he had a hemoglobin content of 11.5 Gm. per hundred cubic centimeters, a red blood cell count of 3,700,000 and a hematocrit value of 39.

CASE 4.—C. T., a 50 year old Barbadian-born Negro, complained of progressive weakness, anorexia, loss of weight and dyspnea for five months. On examination, the patient appeared malnourished, dyspneic and acutely ill. There was a decided pallor of all the mucous membranes as well as a shiny tongue with atrophic papillae. A hemogram revealed a red blood cell count of 1,900,000 and a hemoglobin content of 5.25 Gm. per hundred cubic centimeters. The white blood cell count was 5,350, with 67 per cent neutrophils, 1 per cent eosinophils and 32 per cent

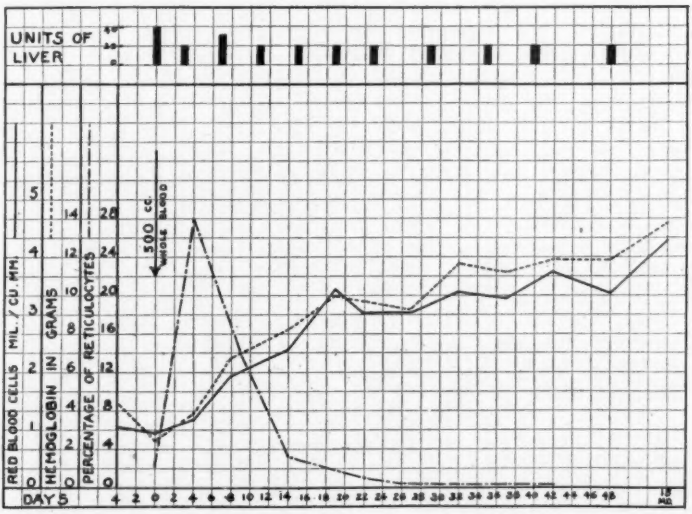

Chart 1.—Hemoglobin content and red blood cell and reticulocyte counts after the institution of liver therapy.

lymphocytes. The volume index was 1.06. The peripheral blood smear revealed considerable anisocytosis and poikilocytosis. Achlorhydria was present. Roentgenograms of the upper gastrointestinal tract were normal. The patient was placed on liver therapy, and a reticulocyte count of 7.6 per cent was observed three days after. Nine days after therapy was begun the reticulocyte count was 3.6 per cent and six days later it was 3.1 per cent. At the conclusion of twenty-six days of liver therapy, the value for the hemoglobin had risen to 9 Gm. and the red blood cell count to 3,500,000. The patient felt clinically well and was discharged to the outpatient department for liver therapy and follow-up. He returned to the clinic occasionally and then ceased coming. He was readmitted with an exacerbation of his anemia and died shortly after.

Necropsy revealed a hemosiderosis of the viscera and a megaloblastosis of the bone marrow. The cause of death was pernicious anemia.

CASE 5.—J. J., a 51 year old Barbadian-born Negro, was admitted to the hospital because of progressive dyspnea and asthenia of one month's duration, complicated by disorientation and semistupor of three days' duration (chart 1). Examination revealed the patient to be poorly nourished and to appear both acutely and chronically ill. The scleras were icteric, and the edges of the tongue were smooth and red. Sensation could not be evaluated because of the patient's confused and disoriented mental condition. Laboratory study revealed a hemoglobin content of 2.9 Gm. per hundred cubic centimeters, a red blood cell count of 920,000 and a hematocrit value of 9.5. The white blood cell count was 5,050, with 54 per cent neutrophils, 45 per cent lymphocytes and 1 per cent eosinophils. The mean corpuscular volume was 103.2 cubic microns, the mean corpuscular hemoglobin 31.5 micromicrograms and the mean corpuscular hemoglobin concentration 30.5 per cent. The peripheral smear revealed anisocytosis and poikilocytosis and no malarial parasites. The reticulocyte count was 2.6 per cent and the icterus index was 15 units. The platelet count was 60,000 per cubic millimeter. The bleeding, coagulation and prothrombin times were normal. Repeated examination of the stools showed them to be normal. The blood calcium was 11 mg. and the nonprotein nitrogen 51.7 mg. per hundred cubic centimeters. Achlorhydria was found after histamine was given. Sternal marrow puncture revealed megaloblastosis, and the picture was interpreted as compatible with a diagnosis of pernicious anemia. The electrocardiogram demonstrated a complete auriculoventricular dissociation. Liver therapy was instituted, and two days after admission 500 cc. of whole blood was given. The value for the hemoglobin rose to 5 Gm. and the red blood cell count to 1,240,000. Four days after liver therapy was started a reticulocyte count of 28 per cent was obtained. The nonprotein nitrogen had fallen to 22 mg. per hundred cubic centimeters. The patient was remarkably improved, and his mental condition appeared normal. The hemoglobin content and the red blood cell count showed a progressive rise while the reticulocyte count approached a normal level. Two weeks after treatment was instituted, the value for the hemoglobin had risen to 7.5 Gm. and the red blood cell count to 2,400,000 whereas the reticulocyte count was 3.1 per cent. The icterus index was now normal. A series of roentgenograms of the upper gastrointestinal tract was made and found to be normal. A repeat electrocardiogram revealed a return to sinus rhythm. One month after his admission the patient felt well and was discharged. His hemoglobin content was 11.7 Gm. per hundred cubic centimeters, the red blood cell count 3,690,000 and the reticulocyte count 0.3 per cent at this time. The patient has been followed for fifteen months, and up to the time of this report he has felt perfectly well, with a hemoglobin content of 13.8 Gm. per hundred cubic centimeters and a red blood cell count of 4,200,000.

CASE 6.—P. P. a 47 year old Colombian Negro, was admitted to the hospital with the complaint of weakness, vertigo, sore tongue and paresthesias in the finger tips for one week. Physical examination revealed the patient to be chronically ill. The scleras were icteric, and the mucous membranes of the conjunctivas and mouth were pale. The tongue was smooth and red. The hemogram showed 6.7 Gm. of hemoglobin per hundred cubic centimeters, with 2,260,000 red blood cells. The white blood cell count was 5,050, and there were 64 per cent neutrophils, 2 per cent eosinophils and 34 per cent lymphocytes in the differential count. The peripheral blood smear revealed pronounced poikilocytosis, anisocytosis and polychromasia. The mean corpuscular volume was 93 cubic microns, the mean corpuscular hemoglobin 29 micromicrograms and the mean corpuscular hemoglobin concentration

31 per cent. The reticulocyte count was 0.1 per cent, and the prothrombin time was normal. The icterus index was 12 and the hematocrit value 21. Examination of the stool disclosed Trichuris trichiura but no occult blood. On gastric analysis, no free acid was found after histamine was given. Roentgenograms of the gastrointestinal tract were normal. The parenteral administration of liver was started. Seven days after this treatment was begun the reticulocyte count reached a peak of 15.1 per cent and thereafter steadily decreased. On the twentieth day of treatment the value for hemoglobin was 12.6 Gm., the red blood cell count 3,530,000 and the icterus index 2. Clinical improvement was striking, with remission of all symptoms. The patient was discharged, and a follow-up examination five months later revealed a hemoglobin content of 13.4 Gm. per hundred cubic centimeters and a red blood cell count of 4,200,000.

CASE 7.—I M., a 55 year old Jamaican-born woman, was admitted to the hospital complaining of progressive dyspnea, orthopnea and dependent edema for one week. The past history revealed intermitttent tenderness and stiffness in both legs for several months. Physical examination revealed a poorly nourished, severely ill woman with acute dyspnea. The skin and mucous membranes were pale, and the veins of the neck were distended. There was dulness at the base of both lungs, and many moist inspiratory rales were heard throughout the pulmonary fields. The blood pressure was 180 systolic and 100 diastolic and the pulse rate 135. The heart was markedly enlarged, and there was a precordial grade III blowing systolic murmur. Ascites was present, and there was edema of all extremities and of the abdominal wall. The hemogram on admission showed 4.4 Gm. of hemoglobin per hundred cubic centimeters, with 1,530,000 red blood cells. The white blood cell count was 10,600, with 53 per cent neutrophils, 2 per cent eosinophils, 44 per cent lymphocytes and 1 per cent monocytes. The presence of anisocytosis and poikilocytosis was revealed in the peripheral blood smear. The patient was treated with oxygen, digitalis, mercurial diuretics and morphine. On the third day in the hospital, while still in congestive heart failure, she received a transfusion of 250 cc. of whole blood, without any appreciable change in the hemoglobin content. Three additional transfusions were given, which resulted in a slight increase in the hemoglobin to 7.0 Gm. and in the red blood cell count to 1,720,000. She regained cardiac compensation, but the severe anemia persisted. Examination of the stools occasionally revealed occult blood, but roentgenologic examination of the gastrointestinal tract disclosed no intrinsic lesion. Gastric analysis showed no free acid after histamine was given. A loss of the vibratory and the position sense in the lower extremities was found. Four weeks after admission the value for hemoglobin was 5.6 Gm. and the red blood cell count 1,350,000. The white blood cell count was 7,100, with a normal differential count, but the anisocytosis and poikilocytosis were still present. The reticulocyte count was 0.1 per cent, and the hematocrit value was 15. The mean corpuscular volume was 118 cubic microns, the mean corpuscular hemoglobin 41 micromicrograms and the mean corpuscular hemoglobin concentration 37 per cent. The platelet count, bleeding and coagulation times and prothrombin time were normal. Liver therapy was begun, and four days later the reticulocyte count had reached 8.1 per cent. This rise increased progressively, so that nine days after treatment was started the reticulocyte count had reached 39 per cent. The reticulocytosis then declined, and twenty days after the beginning of treatment the count had fallen to 0.5 per cent. Eight weeks after therapy was begun the patient felt clinically well. Vibratory and position sense had improved considerably. The value for hemoglobin at this time was 12.6 Gm. and the red blood cell count 4,470,000. She was discharged to be followed as an outpatient.

Case 8.—J. R., 55 year old Barbadian-born Negro, sought admission to the hospital because of progressive asthenia, paresthesias of his lower extremities and vertigo associated with transitory episodes of syncope, all of one week's duration (chart 2). The past history revealed that he had been previously admittted to the hospital for a severe undiagnosed anemia, which responded to liver therapy. He failed to continue specific therapy after his discharge, and this exacerbation had occurred. Examination on admission showed a poorly nourished man with an ataxic gait who appeared chronically ill. The edges of the tongue were smooth and red. There was a loss of position and vibratory sensation. The finger to nose test revealed abnormality, and the Romberg test elicited a positive reaction. The hemoglobin content was 6.5 Gm. per hundred cubic centimeters and the red

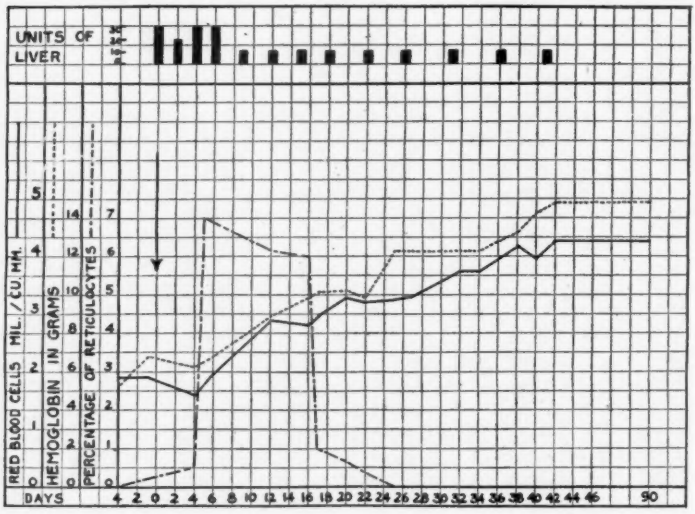
UNITS OF LIVER
RED BLOOD CELLS MIL. / CU. MM.
HEMOGLOBIN IN GRAMS
PERCENTAGE OF RETICULOCYTES
DAYS
4 2 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 90

Chart 2.—Hemoglobin content and red blood cell and reticulocyte counts after the institution of liver therapy.

blood cell count 1,990,000. The white blood cell count was 3,600, with 43 per cent neutrophils, 2 per cent basophils, 2 per cent eosinophils and 53 per cent lymphocytes. The hematocrit value was 17, and the platelet count was 87,000 per cubic millimeter. The mean corpuscular volume was 90 cubic microns, the mean corpuscular hemoglobin 34.2 micromicrograms and the mean corpuscular hemoglobin concentration 38.2 per cent. A blood smear revealed anisocytosis, poikilocytosis and polychromasia; no reticulocytes were evident. The bleeding, coagulation and prothrombin times were normal. The icterus index was normal, as were the stools on repeated examination. No free hydrochloric acid was demonstrable after administration of histamine. A series of roentgenograms of the upper gastrointestinal tract was normal. Sternal marrow puncture revealed megaloblastosis and several multilobed neutrophilic leukocytes, and the picture was interpreted as compatible with pernicious anemia. Liver therapy was begun,

and four days later the reticulocytes numbered 7 per cent. The hemoglobin content and the red blood cell count increased, so that ten days after therapy was initiated they were 8.5 Gm. and 2,980,000 respectively. The reticulocyte count was 4.2 per cent. The patient felt much stronger and was now able to walk unaided. His course became one of steady, progressive clinical and hematologic improvement so that he was able to be discharged six weeks after specific therapy was instituted. His gait was normal, as was the reaction to the Romberg test. The vibratory sensation was still somewhat diminished but was much improved since his admission. The hemoglobin content was 14.8 Gm. per hundred cubic centimeters and the red blood cell count 4,230,000, and no reticulocytes were seen. He has been followed for three months as an outpatient, and his blood picture has remained the same. He has regained almost complete return of his vibratory sensation.

CASE 9.—R. S., a 60 year old Panamanian Negro, was admitted to the hospital with the complaints of progressive weakness and dyspnea of one month's duration. Nine years prior to this admission, a diagnosis of pernicious anemia had been made in another hospital and treatment with liver instituted. He had taken treatment intermittently, but for several months before this admission he had received no liver therapy. Physical examination showed a well nourished and well developed man who appeared chronically ill. The conjunctivas and mucous membranes of the mouth were pale, and the edges of the tongue were smooth. The vibratory sensation was absent in the lower extremities. The hemoglobin content was 5.6 Gm. per hundred cubic centimeters, the red blood cell count 1,260,000 and the white blood cell count 9,200, with 83 per cent neutrophils, 16 per cent lymphocytes and 1 per cent monocytes. A blood smear showed anisocytosis, poikilocytosis and polychromasia. The hematocrit value was 13, the mean corpuscular volume 103 cubic microns, the mean corpuscular hemoglobin 44 micromicrograms and the mean corpuscular hemoglobin concentration 43 per cent. The reticulocyte count was 0.5 per cent, and the icterus index was 15 units. On gastric analysis there was no free acid present after the administration of histamine. On the day after his admission treatment with liver extract was begun. However, by the fourth hospital day the value for hemoglobin had decreased to 4.0 Gm. and the red blood cell count to 818,000. After a transfusion of 500 cc. of whole blood the hemoglobin increased to 8.6 Gm. and the red blood cell count to 2,240,000. Seven days after treatment was started the reticulocyte count reached 16.6 per cent but the hemoglobin content and the red blood cell count decreased. Occasionally, occult blood was found in the stools, but roentgenograms of the gastrointestinal tract were normal. After twelve days of treatment with liver a hemoglobin value of 8.6 Gm. and a red blood cell count of 2,270,000 reflected a beginning response. The reticulocyte count dropped to 1 per cent, and the icterus index returned to normal. Improvement was slow, but after forty-six days of treatment the hemoglobin value was 13.2 Gm. and the red blood cell count 3,820,000. The patient felt well clinically and was discharged to be followed as an outpatient.

CASE 10.—N. P., a 70 year old Barbadian-born Negro, was admitted to the hospital because of progressive weakness. Examination revealed a chronically ill, disoriented, elderly man with a blood pressure of 108 systolic and 54 diastolic. Notable glossitis was present, and a systolic blowing precordial murmur was heard. Laboratory study revealed a hemoglobin content of 3 Gm. per hundred cubic centimeters, a red blood cell count of 1,020,000 and a white blood cell count of 3,700, with 60 per cent neutrophils, 4 per cent eosinophils and 36 per cent lymphocytes. The hematocrit value was 11, and the mean corpuscular volume was 104

cubic microns. The mean corpuscular hemoglobin was 33 micromicrograms and the volume index 1.09. The platelet count was 138,000 per cubic millimeter, and the reticulocyte count was 1 per cent. The icterus index was 8 units. No free hydrochloric acid was found after histamine was given. The stools were normal. Poor cooperation made gastrointestinal roentgenograms unsatisfactory. Sternal marrow puncture revealed an increase in megaloblasts and in multilobed neutrophils, which was interpreted as being compatible with pernicious anemia. Three days after liver therapy was instituted the reticulocyte count rose to 5 per cent and four days later to 20 per cent. The peak of the reticulocytosis was noted ten days after treatment was begun, when the count reached 35 per cent. The patient showed a corresponding clinical improvement, with his mental condition becoming normal. Liver therapy was continued, and there was a good hematologic response. One month after therapy was started the hemoglobin content had reached 9 Gm. per hundred cubic centimeters and the red blood cell count 3,000,000. The reticulocyte count was now 1.5 per cent. The patient was still in the hospital under treatment at the time of this report.

COMMENT

In the "Biology of the Negro" Lewis[11] states: "Disease tends to prove the kinship of the different races of man but at the same time clearly demonstrates some of their differences. There is no illness which affects one race that may not also affect every other race although the manifestations of an illness may vary widely among races both qualitatively and quantitatively." This statement reflects our views on the incidence and occurrence of pernicious anemia in the tropical Negro. The true incidence of the disease in the tropics doesn't seem to have been well presented in the sparse literature available. Some of the cases described by Willis[9] as cases of "tropical macrocytic anemia" seem to fulfil the criteria for the diagnosis of pernicious anemia. Further study will probably reveal that "tropical macrocytic anemia" can be organized into several classifications, pernicious anemia being one of them.

It was virtually impossible to obtain complete and accurate genealogic data on our patients, and hence there was no certainty as to the admixture of Negro and Caucasian blood. Nine of our 10 patients came from the islands of the West Indies group, a native Negro habitat, and they all had Negro parents. The tenth was a dark-skinned Colombian of mixed dark Colombian and West Indian parentage. Clinically and anthropologically they were considered Negroes.

Six of the 10 patients have been observed personally by us and 4 of them followed as outpatients for a period ranging from three to fifteen months. We feel that the diagnostic criteria employed in our cases were sufficiently rigid to warrant their acceptance as instances of true perni-

11. Lewis, J. H.: The Biology of the Negro, Chicago, University of Chicago Press, 1942.

cious anemia. The 2 cases in which the diagnosis was made after death give credence to the idea that the disease exists among tropical Negroes.

Willson and Evans[12] concluded that pernicious anemia was milder in Negroes, but Schwartz and Gore[6] couldn't corroborate this. In our study no remarkable differences were demonstrable between the expression of the disease in the tropical Negro and that in other persons except for the absence of the classic lemon-colored skin. The hemoglobin value and the red blood cell count rarely attained levels of 15 Gm. and 5,000,000 respectively, such as are occasionally seen in the Caucasian patient with this disease.

SUMMARY AND CONCLUSIONS

1. Ten cases of pernicious anemia in the tropical Negro are presented.

2. No essential differences were brought out in the manifestations of the disease in Negroes and in other races.

3. Pernicious anemia does occur in tropical natives, and further study and increased awareness will cause it to be more frequently recognized.

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12. Willson, C. R., and Evans, F. A.: Pernicious Anemia in Johns Hopkins Hospital from 1918-1922, Bull. Johns Hopkins Hosp. **35**:38, 1924.

CLINICAL OBSERVATIONS IN CASES OF MASSIVE MYOCARDIAL INFARCTION

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MYOCARDIAL infarction is a dramatic episode in the course of coronary artery disease, but it is often thought of in terms of a disease entity with its own course, prognosis and treatment. With the occurrence of myocardial infarction, a new factor is introduced into the course of coronary artery disease with myocardial ischemia, namely, gross and irreparable destruction of a portion of the cardiac muscle. This damage to the myocardium determines the immediate prognosis and the ultimate outcome entirely independently of the degree and progression of coronary arteriosclerosis. Thus, the size of the area of the destroyed muscle is one of the important factors in the prognosis, yet little investigative work has been done in estimation of the size of a myocardial infarct during life.

In terms of ordinary clinical thinking, a severe attack of pain with fully developed clinical signs of myocardial infarction is usually considered as evidence of a large infarct, while milder initial attacks with less pronounced clinical and electrocardiographic signs are thought to indicate small infarcts of the myocardium. This view, however, represents speculation rather than knowledge based on clinical-pathologic correlation.

The main difficulty in approaching the problem of correlating clinical features with the anatomic findings in myocardial infarction lies in the determination of the size of the infarct at autopsy. Massive necrosis involving large sections of the myocardium can be distinguished without much difficulty, but only a detailed study of the myocardium requiring special procedures enables the pathologist to estimate the degree of myocardial involvement in smaller infarcts. It was felt, then, that useful information could be obtained by a clinical study of cases of massive infarcts of the heart, representing the most severe anatomic damage to the cardiac muscle. While this approach is only a step in the direction

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of closer clinical-pathologic correlation of myocardial infarction, it obviates the use of elaborate setups required for the study of small infarcts.

This report is based on 28 unselected cases of myocardial infarction in which the pathologic diagnosis of "recent massive myocardial infarct" was made at autopsy. It covers all cases in which this diagnosis was made in the eight year period of 1937 to 1944 in the files of the department of pathology except 8 cases of massive myocardial infarction in which clinical records were inadequate for the study. These represent 21 per cent of the total of 135 cases of recent myocardial infarction found during this period.

Pathologic data consisted of a complete and detailed description of the heart, coronary arteries and other organs affected directly and indirectly by the disease, each of which was examined grossly and microscopically. Clinical records were carefully studied with special reference to the patients' past history, the initial attack of the recent myocardial infarction, the symptomatology and the course of the attack, the laboratory and electrocardiographic findings and the mode of death.

COMMENT

The important features of acute myocardial infarction can be divided into four groups: (*a*) the initial attack (pain, dyspnea and associated symptoms); (*b*) the effect of the infarct on the circulation (heart failure, shock and drop in blood pressure); (*c*) the constitutional reaction to tissue destruction (fever, leukocytosis and increased sedimentation rate), and (*d*) the electrocardiographic changes of myocardial infarction. If a close correlation existed between the extent of myocardial infarction and its clinical features, then one would expect to find a uniformity in the severity of the clinical features in cases of massive myocardial infarction.

In this series, pain (the fundamental symptom of myocardial ischemia) was present in only 22 of the 28 cases and was severe in less than half of the cases. Dyspnea was often present and was more prominent in cases in which the pain was mild or absent. In only 1 case were both pain and dyspnea recorded as severe. Nausea with vomiting and collapse was rather infrequent.

Circulatory derangement was not severe in all cases. Left ventricular failure was present in most cases, but a severe degree of it was found in 8. Right ventricular failure and shock were infrequent. Half of the patients lived one week or more after the initial attack, and many of these died not as a result of severe circulatory insufficiency but as a result of secondary complications. These occurred frequently in patients making apparently satisfactory progress.

*Summary of Clinical and Pathologic Signs in 28 Cases of Massive Myocardial Infarction**

No.	Age, Sex	Summary of History	Blood Pressure	Temperature	Left Ventricular Failure	Right Ventricular Failure	Shock	White Blood Cell Count	Sedimentation Rate	Electrocardiogram	Duration, Days	Pathologic Findings	Immediate Cause of Death
1	63 M	Moderately severe attack of substernal pain, nausea, vomiting, then severe dyspnea, of 24 hours' duration	80/60	--	+++	--	--	33,200	--	--	2	Thrombus in the left coronary artery; recent massive myocardial infarct of large part of left ventricle	--
2	60 M	Moderately severe pain, constriction in anterior part of the chest, severe dyspnea of 12 hours' duration	110/75	38C. (100.4F.)	+++	--	--	13,200 (2) 11,500 (5)	25mm. W(5)	Low voltage; elevated $S\text{-}T^4$, deep Q^4, depressed $S\text{-}T^2$, S-T3 (3)	3	Thrombus in left anterior coronary branch; recent infarct of almost entire apex of left ventricle	--
3	49 M	Pain in right side of chest, with cough, night sweats, mild dyspnea of 48 hours' duration	105/70, then systolic pressure below 100	37 to 39C. (98.6 to 102.2F.)	+	--	--	13,700	22mm. W	Normal (2); T1 and T4 deeply inverted, T2 flat (21)	26	Thrombus in left anterior coronary branch; recent infarct of apex of left ventricle and entire septum; multiple emboli	Femoral embolism
4	50 M	Attack of faintness, dizziness and cold perspiration of few hours' duration; for a year suffered from mild epigastric pressure on exertion	80/60	38C. (100.4F.)	--	--	+++	28,200	7mm. W	Atypical bundle branch block; no S-T deviation (3)	6	Thrombus in left anterior coronary branch; recent infarct of anterior wall of left ventricle and 2/3 of septum; multiple pulmonary infarcts	Multiple pulmonary emboli
5	66 M	Moderately severe substernal pain of 16 hours' duration, followed by cough, dyspnea	130/90	38C. (100.4F.)	+++	++	--	--	18mm. W	Classic Q1T1 type myocardial infarct pattern; later right axis deviation; low voltage	13	Recent thrombus in left anterior coronary branch; old infarct, 6x4 cm., of the posterior wall; recent infarct of anterolateral wall, left ventricle and 1/3 of septum	
6	65 M	In hospital for carcinoma of prostate: mild exertional chest pain developed, then a severe attack of pain across lower part of chest, with dyspnea and weakness	80/40	--	++	--	+	--	--	--------	1	Thrombus in left circumflex coronary branch; recent infarct of posterior and lateral wall of left ventricle	--
7	56 M	In hospital because of rectal bleeding, severe attack of pain in the anterior part of the chest with dyspnea, anxiety and cold perspiration	170/120	Normal	--	--	--	15,900	32mm. W(6)	Small Q^4; $S\text{-}T^2$, ST^4, slightly elevated; $S\text{-}T^4$ elevated, T1, T4 inverted (3)	15	Thrombus in left anterior coronary branch; recent infarct of distal half of the left ventricle, with a more recent hemorrhage in apical area	Sudden death

No.	Age, Sex	Summary of History	Blood Pressure	Temperature	Left Ventricular Failure	Right Ventricular Failure	Shock	White Blood Cell Count	Sedimentation Rate	Electrocardiogram	Duration, Days	Pathologic Findings	Immediate Cause of Death
8	57 M	Mild substernal pain of 36 hours' duration; attack of severe dyspnea, cough, frothy sputum on admission to hospital; exertional angina for two years	100/70	38C. (100.4F.)	++	--	+++	--	--	Q waves in leads I, II, III; elevated S-T segments and inverted T-waves in leads I, II, IV (2), then wide and vibratory QRS complexes developed	4	Thrombus in left anterior coronary branch; recent massive myocardial infarct of anterolateral part of left ventricle, anterior part of right ventricle and lower part of the septum	--
9	73 F	Attack of severe precordial pain of three hours' duration	130/90	37.2C. (98.9F.)	+++ (late)	--	--	9,000 (2) 18,000 (7)	49mm. (C)	S-T segments depressed in all leads (2). Later S wave appeared in leads II and III, T1 became inverted (4)	8	Thrombus in left anterior and left circumflex coronary branches; recent infarct of most of anterolateral wall of left ventricle, basal portion of septum; old infarct, 7x2cm., in the posterior wall of left ventricle	
10	68 F	Severe epigastric and lower substernal pain with repeated vomiting and palpitation of 24 hours' duration	105/70	38.5C. (101.3F.)	+	--	--	12,300	21 mm. (W)	Broad S wave type, right bundle branch block with absent R4, elevated S-T4 (2)	3	Thrombus in left coronary artery; recent infarct of lower 2/3 of septum, anterior portion of left ventricle and entire apex	Sudden death
11	67 F	Three days prior to admission, severe substernal pain, nausea, vomiting; similar attack 6 years previously; in bed 3 months	110/80	38.8C. (101.8 F.) later 39 to 40C. (102.2 to 104 F.)	+++	--	--	13,000 (3) 20,000 (5)	46 mm. (C)	Left axis deviation; depressed S-T1,2,4 inverted T1 (2), less marked S-T deviation (6); normal axis, normal lead IV (9)	10	Thrombus in left circumflex coronary branch; old thrombus of left anterior branch; recent infarct, 9x9 cm., most of posterior wall of left ventricle; old infarct, 5x12 cm., in anterior wall of left ventricle	
12	54 M	Severe pain in anterior part of chest of 48 hours' duration; similar attack 7 years previously untreated; last 6 months exertional anginal attacks	98/78	38 to 39 C. (100.4 to 102.2 F.)	+	--	++	9,000	--	Left axis deviation; deep Q2, Q3; slight elevation of S-T2, S-T3, inverted T2,3 (3)	4	Thrombus in left coronary artery; recent infarct, 12x15 cm., of distal half of septum and anterior wall of left ventricle; part of posterior wall of left ventricle; scar in left ventricle wall	
13	67 M	Severe pain in anterior part of chest and left arm, dyspnea, nausea and vomiting of 24 hours' duration	90/70	38.5 C. (101.3 F.)	+++	--	+	15,000	32 mm. (W)	Wide QRS complexes with prominent S waves, slight elevation of S-T4 (4)	4	Thrombus in left anterior coronary branch; recent infarct, 10x12 cm., of anterior wall of left ventricle and entire septum	
14	77 F	Severe pain in anterior part of chest and left shoulder, followed by severe dyspnea of several hours' duration	140/90	38 C. (100.4 F.)	+++	++	--	16,000	--	--------	3	Severe coronary sclerosis, no thrombus found; recent infarct of lower half of septum and most of anterior wall of left ventricle	

*Summary of Clinical and Pathologic Signs in 28 Cases of Massive Myocardial Infarction**—Continued

No.	Age, Sex	Summary of History	Blood Pressure	Temperature	Left Ventricular Failure	Right Ventricular Failure	Shock	White Blood Cell Count	Sedimentation Rate	Electrocardiogram	Duration, Days	Pathologic Findings	Immediate Cause of Death
15	68 M	Nightly attacks of severe dyspnea for one week	140/80	38 C. (100.4 F.)	+	--	--	7,900	--	Normal QRS complexes; inverted T waves in leads I, II and III; normal lead IV (3)	7	Thrombus in right coronary artery; recent massive myocardial infarct of most of posterior wall of left ventricle	Sudden death
16	56 M	Attack of severe pain in upper abdominal area with nausea and vomiting of several hours' duration	110/80	(39 C. (102.2 F.)	--	--	++	26,000	--	Classic sequence of patterns of posterior myocardial infarction	20	Thrombus in right coronary artery; recent infarct of entire posterolateral wall of left ventricle	Gastrointestinal hemorrhage
17	41 M	Series of attacks of pain in the anterior part of chest radiating to both elbows, of one week's duration; most severe for 6 hours, with vomiting; at age 29, similar attack	160/100	37.5 C. (99.5 F.)	+	--	--	14,900	14 mm. (W) (2) 29 mm. (W) (12)	Left axis deviation with prominent Q2 and QS3; normal S-T (3); no change (5, 7)	21	Thrombus in left circumflex coronary branch; old thrombus of left anterior coronary branch; recent infarct of anterior and posterior wall of left ventricle; scar in apex and lower 2/3 of septum	Cerebral embolus
18	82 F	Sudden attack of severe dyspnea, nausea, vomiting and cough with frothy sputum—3 hours' duration	210/110	37.5 C. (99.5 F.)	++	--	--	16,800	--	Normal QRS complexes; inverted T waves in leads I, II, III and IV; auricular fibrillation (2)	3	Incomplete occlusion of left anterior coronary branch; recent infarct of large part of posterior wall, portions of anterior wall and septum	Cardiac rupture
19	79 M	While in hospital recovering from prostatectomy, had sudden attack of severe dyspnea, cyanosis, apprehension and cough	200/100	--	+++	--	--	--	--	Normal QRS complex; depressed RS-T segment in leads I, II and IV; normal T waves (2)	8	Thrombus in right coronary artery, old thrombus in left anterior coronary branch; recent infarct of posterolateral wall of left ventricle; scar (small) at apex	
20	73 M	Attack of severe dyspnea of 24 hours' duration; within past two weeks, several mild attacks of nocturnal dyspnea	140/100 then 100/65	39 C. (102.2 F.)	++	++	--	20,000 (2) 15,000 (5)	--	Marked left axis deviation; small R4; T1 inverted (2)	8	Thrombus in left circumflex coronary branch; recent infarct of most of left ventricle	Multiple emboli systemic and pulmonary
21	66 M	Attack of severe pain in anterior part of the chest, left scapula, neck, both arms—3 hours' duration; patient known to have hypertension	140/100	37.5 C. (99.5 F.)	+	--	--	17,800	--	Left axis deviation, absent R4, markedly elevated RS-T segment in leads I and IV (2)	3	Thrombus in left anterior coronary branch; recent infarct of anterior 2/3 of left ventricle wall, entire apex and lower septum	Cardiac rupture

No.	Age, Sex	Summary of History	Blood Pressure	Temperature	Left Ventricular Failure	Right Ventricular Failure	Shock	White Blood Cell Count	Sedimentation Rate	Electrocardiogram	Duration, Days	Pathologic Findings	Immediate Cause of Death
22	54 M	Collapsed three weeks prior to admission; severe dyspnea and orthopnea, which persisted	110/70 (20)	37.5 C. (99.5 F.)	+++	--	--	5,600 (20)	--	--------	22	Thrombus in left anterior coronary branch; recent massive myocardial infarct of most of anterior wall of left ventricle, 2/3 of septum	
23	60 M	Severe epigastric pain with extreme dyspnea of 3 hours' duration; milder attacks of pain for few weeks	115/80	(38 C.) (100.4 F.)	+++	--	--	12,400	--	Left axis deviation, flat T1 (2)	2	Thrombi in left anterior coronary branch and left circumflex coronary branch; recent infarct of most of posterolateral wall of left ventricle	Sudden death
24	76 M	Excruciating pain in upper abdominal and lower chest areas radiating to both arms, nausea and vomiting of 12 hours' duration	80/60	38 C. (100.4 F.)	+	--	+ (late)	18,000	20 mm. (W)	Left bundle branch block, with small Q1,4 slight elevation of S-T2,3 (2)	3	Thrombus in left circumflex coronary branch, old thrombus in left anterior coronary branch; recent infarct of posterior half of left ventricle	
25	66 M	Attack of moderately severe burning pain in anterior part of chest, with weakness—24 hours' duration; patient known to have hypertension	110/70	38 C. (100.4 F.)	+	--	--	11,400 (4) 15,200	21 mm. (W)	Q waves present in leads I, II, III; elevation of S-T segment in leads I, II, and IV; T3 inverted (3); T waves inverted in all 4 leads (7)	13	Thrombus in left anterior coronary branch; recent infarct of entire anterior wall of left ventricle	Perforation of heart
26	63 M	Series of attacks of severe pain in anterior part of chest over period of 4 days	130/90	39 C. (102.2 F.)	++	--	--	19,800	10 mm. (W)	Atypical bundle branch block, no S-T deviations, no change in pattern (2,6)	12	Thrombus in left anterior coronary branch; recent infarct of anterior 2/3 of septum, most of anterior wall of left ventricle and some of right ventricle	Empyema
27	56 M	Attack of severe chest pain, dyspnea, nausea and vomiting of 3 hours' duration; similar attack 9 years previously	130/90	39 C. (102.2 F.)	++	+	--	15,300	31 mm. (W) (5)	Left axis deviation; prominent Q2, QS3, inverted T2, T^3 (2)	20	Thrombus in right coronary artery, old thrombus in left anterior coronary branch; recent infarct of all posterolateral wall of left ventricle; scar at apex	Cerebral embolism
28	52 M	Attack of severe pain in anterior part of chest of 4 hours' duration; lesser attacks for several weeks; 6 months previously had myocardial infarction	160/110	38.5 C. (101.3 F.)	+	--	--	24,000 (2)	17 mm. (W)	Left axis deviation; deep Q2, Q3, elevated S-T segment in leads I, II and III, inverted T1,4 (2)	3	Thrombus in left circumflex coronary branch, old thrombus in left anterior coronary branch; recent infarct of entire distal half of left ventricle, scar in apical portion of left ventricle	

Fever was present in 27 of the 28 cases, but the elevation of temperature was on the average mild. In only 10 cases did the temperature reach or exceed 39 C. (102.2 F.). A high degree of leukocytosis (20,000 cells or over) was found in less than half of the cases in which blood counts were recorded. Also, the sedimentation rate was not persistently elevated.

Electrocardiographic findings in the 24 cases in which records were available had to be interpreted with great care, because only four lead electrocardiograms were available. Present day emphasis on exploration of the thoracic wall with semidirect leads makes four lead electrocardiography seem incomplete, yet the three standard limb leads are still the basis and the essential part of the electrocardiogram and are of particular value in myocardial infarcts of the posterior wall. In this series 4 patients showed the classic pattern of myocardial infarction, 5 had atypical changes, with RS-T deviation and T wave changes supporting the clinical diagnosis of myocardial infarction, 3 had depression without elevation of the RS-T segments, making the record equivocal, 7 had no RS-T changes whatsoever and only equivocal T wave changes and, finally, 5 had bundle branch block patterns with or without displacement of the RS-T segments. It is striking that in this small series of cases of massive myocardial infarcts the classic patterns of acute myocardial infarction in the standard limb leads were uncommon; atypical and even nondiagnostic patterns were present in the majority of cases, with almost all tracings taken at the time when maximum changes were to be expected. Doubtless, serial precordial leads taken in some of these cases would have shown changes indicative of myocardial infarction which were not present in the standard four lead electrocardiogram, but this would not have altered the general trend of the electrocardiographic findings.

In order to estimate the over-all severity of the clinical picture of myocardial infarction, an arbitrary scoring was devised. With the omission of electrocardiographic signs, which could not be scored satisfactorily, the three groups of features of myocardial infarction (initial attack, circulatory derangement, constitutional reactions) were scored thus: 1, mild or absent; 2, moderately severe, and 3, severe. Thus the mildest manifestations of myocardial infarction were scored as 3 and the most severe as 9. As a result of this scoring 6 patients were classified as having mild disease (scores 3 and 4); 14 patients as having

Footnote for Table.

*W indicates Wintrobe method and C Cutler method. Number in parentheses following various laboratory readings and electrocardiographic descriptions indicates the number of days after the presumed onset of the recent myocardial infarction. "Duration" indicates the time elapsing between the presumed onset of myocardial infarction and death. "Sudden death" is recorded only for patients not appearing seriously ill and is presumed to be caused by ventricular fibrillation.

moderately severe disease (scores 5 and 6) and 8 as having severe disease (scores 7, 8 and 9). Three patients had a score of 3, and 2 patients were given a score of 9.

This analysis is perhaps the best way of showing that massive myocardial infarction does not necessarily run the course of a severe, uniformly fatal illness. It also suggests that the relationship between the severity of clinical manifestations and the extent of myocardial infarction is far less simple than is generally assumed. It is evident that none of the various clinical features of myocardial infarction has occurred in a characteristic form, nor has an unusual severity of them been frequent enough to be of aid in the diagnosis of massive myocardial infarction.

The severity of the initial attack, the effect of the infarction on the circulation and the constitutional reactions to it are obviously affected by additional factors other than the size of the necrotic area of the myocardium. It is not clear what the nature of these factors is. It was shown in another report[1] that patients with preexisting cardiac disease, such as hypertension with cardiac hypertrophy or old myocardial scars from previous infarcts, do not respond differently to a new infarction than those who had no evidence of myocardial disease prior to the fatal infarction. This is fully confirmed in this series. It has also been suggested that the degree of coronary arteriosclerosis bears no obvious relationship to the immediate prognosis of acute myocardial infarction. Individual variations in the response to myocardial ischemia and injury and in the ability to compensate for its effect on the circulation may play an important role in explaining the discrepancy between the degree of myocardial damage and the clinical manifestation and course. An interesting possibility is suggested by the work of Rosenbaum, Johnston and Wilson,[2] who presented electrocardiographic evidence that myocardial infarction may develop over a period of a few days. A gradually developing myocardial infarction or a smaller infarct with a secondary extension may perhaps have a less profound effect on the circulation and give rise to fewer symptoms and constitutional reactions than myocardial necrosis of equal extent developing all at once. In the correlation of clinical features with pathologic findings of myocardial infarction, it should be noted that Robb and Robb[3] and Lowe and Wartman[4] expressed

1. Selzer, A.: The Immediate Sequelae of Myocardial Infarction: Their Relation to the Prognosis, Am. J. M. Sc. **216**:172 (Aug.) 1948.

2. Rosenbaum, F. F.; Wilson, F. N., and Johnston, F. D.: Changes in the Precordial Electrocardiogram Produced by the Extension of Anteroseptal Myocardial Infarction, Am. Heart J. **30**:11 (July) 1945.

3. Robb, J. S., and Robb, R. C.: Localization of Cardiac Infarcts in Man: I. Comparison of Anterior-Posterior with Muscle Bundle Modes of Localization, Am. J. M. Sc. **197**:7 (Jan.) 1939; II. Twenty-Nine New Cases of Muscle Bundle Localization with Postmortem Confirmation, ibid. **197**:18 (Jan.) 1939.

4. Lowe, T. E., and Wartman, W. B.: Myocardial Infarction, Brit. Heart J. **6**:115 (July) 1944.

the opinion that some specific myocardial muscle bundles may have important functions. However, this factor need not be considered in the interpretation of massive myocardial infarction in which all layers of the myocardium were destroyed over large areas.

It is shown that typical electrocardiographic patterns are not a common feature of massive myocardial infarcts and presumably occur more often in smaller infarcts. This is best explained by assuming that a simultaneous involvement of various regions of the heart causes cancellation of certain electrocardiographic changes; involvement of sections of the heart, the injury to which would be expected to alter the electrocardiogram in the opposite directions, is much more likely to occur in massive infarcts than in small ones. In connection with this, it is well to point out that statistical studies have repeatedly shown that myocardial infarction which produces atypical patterns in the electrocardiogram offers a poorer prognosis than that in which typical patterns are present.[5] Findings reported here may be considered an anatomic confirmation of this observation.

The practical implications of the observations presented in this report are obvious. Not only have no characteristic features of massive myocardial infarction been demonstrated, but it was shown that massive myocardial infarcts may be masked by a mild onset, absence of alarming signs, low grade constitutional reactions and equivocal laboratory and electrocardiographic findings. Symptoms of massive myocardial infarction may be so benign that doubt may even exist as to whether myocardial infarction has occurred at all in a patient with coronary artery disease.

SUMMARY AND CONCLUSIONS

A series of 28 cases of recent massive myocardial infarction found at autopsy was studied and the symptomatology, clinical course and laboratory and electrocardiographic findings presented.

The initial attack, the effects on the circulation and the constitutional reactions of acute myocardial infarction were not of uniform severity in this series. The predominance of mild and moderately severe clinical manifestations over extremely severe ones in proved cases of massive myocardial infarction suggests that there is no close correlation between the clinical picture and the anatomic changes. In spite of severe damage to the myocardium, several patients showed no evidence of serious circu-

5. (*a*) Barnes, A. R.: Electrocardiogram in Myocardial Infarction: A Review of One Hundred and Seven Clinical Cases and One Hundred and Eight Cases Proved at Necropsy, Arch. Int. Med. **55**:457 (March) 1935. (*b*) Rosenbaum, F. F., and Levine, S. A.: Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction: I. Immediate Prognosis, ibid. **68**:913 (Nov.) 1941. (*c*) Woods, R. M., and Barnes, A. R.: Factors Influencing Immediate Mortality After Acute Coronary Occlusion, Am. Heart J. **24**:4 (July) 1942.

latory insufficiency and presumably would have recovered had they not succumbed to secondary complications which developed in the course of acute myocardial infarction.

Four lead electrocardiographic studies were not appreciably helpful in the diagnosis of massive myocardial infarction. Atypical patterns occurred in the majority of cases, and in some of them only minor deviations from normal were present.

The practical significance of these findings lies in the demonstration of the fact that massive myocardial infarction may cause benign clinical symptoms, suggesting only minor damage to the myocardium, or may even make the presence of a recent infarct questionable.

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PRIMARY MALIGNANT DISEASE OF THE SMALL BOWEL

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PRIMARY malignant disease of the small bowel is comparatively rare. As Morison[1] has stated, "For the area exposed, the small intestine enjoys as great an immunity from new growth as any part of the body." During the past few years, this condition has aroused increasing interest. The chief difficulty has been early diagnosis, but with the better technics now available for the roentgenologic investigation of the small intestine, its presence can be demonstrated sufficiently early to offer hope of successful surgical intervention. Awareness of the possibility remains, however, the prime necessity for its recognition and offers a challenge for early diagnosis. The present communication is a report of 15 cases encountered at City Hospital, Welfare Island, and 2 cases from other sources. They are separated into three groups, i.e., cases of carcinoma, cases of carcinoid or argentaffinoma and cases of lymphosarcoma, because of the differences in pathologic and clinical features. Carcinoma primary in the papilla or ampulla of Vater is excluded. The term lymphosarcoma is used to include malignant lymphocytoma and reticulum cell sarcoma. The data on the cases are summarized in table 1.

Tumors of the small bowel are most frequently benign.[2] Of the malignant tumors, carcinoma is usually believed to be more common than

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1. Morison, J. E.: Brit. J. Surg. **29**:139-153, 1941.

2. (*a*) Raiford, T. S.: Tumors of Small Intestine, Arch. Surg. **25**:122-177 (July); 321-355 (Aug.) 1932. (*b*) Good, C. A.: Tumefactive Lesions of Small Intestine, J.A.M.A. **117**:923-926 (Sept. 13) 1941. *(c)* Cohn, S.; Landy, J. A., and Richter, M.: Tumors of Small Intestine, Arch. Surg. **39**:647-666 (Oct.) 1939.

sarcoma,[3] although some observers[4] have found sarcoma to be more frequent. The argentaffinomas occupy a place in between the other types.[5] They are all comparatively rare and comprise about 0.025 per cent of all cancers.[6] The late statistics are given in table 2.

Carcinoma of the small bowel comprises about 3 per cent of gastrointestinal carcinomas and is much less common than carcinoma of the large bowel.[7] Lieber and Stewart[8] accepted 35 cases of suprapapillary carcinoma as authentic and 12 as probable. Ruden[9] increased the number to 59. Felsen and Wolarsky[10] collected 47 cases of infrapapillary duodenal lesion, including 1 of their own. It is more difficult to estimate the number of lesions involving the second part of the duodenum because frequently a clear distinction is not made between primary and secondary lesions. Up to 1943, less than 300 cases of carcinoma of the small bowel had been reported.[11] To these, 64 can be added,[12] including the present series. The cases of Nelson,[13] Cohn[14] and Child[15] are questionable. These data suggest that an actual increase is occurring in the incidence of carcinoma of the small bowel. It is

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3. (*a*) Warren, R. F.: Canad. M. A. J. **51**:451-457, 1944. (*b*) Shallow, T. A.; Eger, S. A., and Carty, J. B.: Am. J. Surg. **69**:372-383, 1945. (*c*) Swenson, P. C.: Rev. Gastroenterol. **10**:77-91, 1943. (*d*) Cameron, A. L.: Ann. Surg. **108**:203-220, 1938. (*e*) Medinger, F. G.: Surg., Gynec. & Obst. **69**:299-305, 1939. (*f*) Fraser, K.: Brit. J. Surg. **32**:479, 1945. *(g)* Good.[2b]

4. Mayo, C. W., and Nettrour, W. S.: Surg., Gynec. & Obst. **65**:303-309, 1937. Raiford.[2a]

5. (*a*) Horsley, J. S.: Carcinoma of Jejunum and of Ileum, J.A.M.A. **117**:2119-2123 (Dec. 20) 1941. (*b*) Swenson.[3c] Cameron.[3d]

6. Mateer, J. G., and Hartman, F. W.: Primary Carcinoma of Duodenum: Clinical and Pathologic Aspects, with Differential Diagnosis, J.A.M.A. **99**:1853-1859 (Nov. 26) 1932.

7. Howard J. W.: Am. J. M. Sc. **206**:735-745, 1943. Mayo and Nettrour.[4]

8. Stewart, H. L., and Lieber, M. M.: Carcinoma of Suprapapillary Portion of Duodenum, Arch. Surg. **35**:99-129 (July) 1937.

9. Ruden, S. J.: Primary Carcinoma of Duodenal Bulb, Arch. Path. **43**:616-619 (June) 1947.

10. Felsen, J., and Wolarsky, W.: Primary Infrapapillary Adenocarcinoma of Duodenum, Arch. Path. **36**:428-431 (Oct.) 1943.

11. McDougal, W. J.: Am. J. Surg. **66**:119-122, 1944.

12. (*a*) Bottsford, J. W., and Seibel, R. E.: New England J. Med. **236**:683-694, 1947. (*b*) Emmet, J. M., and Dreyfuss, M. L.: Ann. Surg. **123**:859-865, 1946. (*c*) Ehrlich, J. C., and Hunter, O. B.: Surg., Gynec. & Obst. **85**:98-106, 1947. (*d*) Shallow, T. A.; Eger, S. A., and Carty, J. B.: Surgery **16**:939-946, 1944. (*e*) Mulligan, R. M.: Adenocarcinoma of Jejunum Associated with Hyperplasia of Parathyroid Glands and Generalized Osteoporosis, Arch. Path. **40**:182-186 (Sept.) 1945 (*f*) Warren.[3a] (*g*) Shallow.[3b] (*h*) Swenson.[3c] (*i*) Howard.[7]

13. Nelson, H.: Minnesota Med. **28**:396-398, 1945.

14. Cohn, I.: Ann. Surg. **119**:342-350, 1944.

15. Child, C. G., III: Ann. Surg. **118**:838-843, 1943.

TABLE 1.—*Clinical and Pathologic Data in Cases Observed*

Case No.	Clinical Features	Pathologic Process	Metastasis
1*	W.M. 34. Onset with substernal, epigastric and general abdominal pain and constipation; sudden episode in 6 months of severe epigastric pain; persistent vomiting subsequently; weight loss, melena, slight anemia, marked epigastric tenderness; stenotic lesion of duodenum on fluoroscopy; total duration, 1 year	Suprapapillary carcinoma	None
2†	W. F., 70. Onset with moderately severe upper abdominal pain; similar attack in 2 months, with mild jaundice; third attack 1 year later, with palpable mass; resection; living 1 year later; clinical evidence of metastasis	Carcinoma of the mesial wall of the second part of the duodenum	Regional lymphatic vessels; invasion of contiguous pancreatic region
3	W. M., 63. Two years of postprandial pain and late jaundice, vomiting, clay-colored stools, weight loss; deep jaundice, moderate anemia, narrowed duodenum in roentgenograms; cholecystojejunostomy; recurrence of jaundice; death; autopsy; total duration, 2 years, 3 months	Infrapapillary carcinoma	Regional lymphatic vessels; invasion of contiguous pancreatic region
4	W. M., 70. Ten year history of ulcer; one period of upper abdominal and retrosternal pain; examination noncontributory; 5½ years later history of melena for 3 years, abdominal pain for 3 months, loss of weight, alternating diarrhea and constipation; moderate abdominal rigidity, right upper quadrant tenderness, deformed duodenum; pulmonary tuberculosis; death from pulmonary and ileal tuberculosis; autopsy	Infrapapillary carcinoma	Regional lymphatic vessels; invasion of contiguous pancreatic region
5‡	W. M., 46. Onset with listlessness for 1/2 year, then increased listlessness, severe anemia, upper abdominal pain, slight weight loss; deformity at ligament of Treitz and signs of slight retention in roentgenograms; resection; living 1 year later apparently free of disease	Carcinoma of the jejunum near the ligament of Treitz	None
6	W. F., 77. Admitted in extremis; no history of gastro intestinal disturbance; death in 4½ hours from acute pneumonia and endocarditis; autopsy; small carcinoma of hepatic flexure without metastasis	Carcinoma of upper jejunal area	None
7	W. M., 68. Sudden onset of severe periumbilical pain, vomiting, constipation; several years of burning epigastric pain; three years previously, 6 weeks of severe constipation followed by progressive weight loss; palpable mass; midjejunal obstruction; resection; further course unknown	Carcinoma of middle jejunal area	?
8	W. F., 64. Sudden attack of upper abdominal pain, slight icterus, slight abdominal distention, spasticity, rebound tenderness, anemia; improvement in 3 weeks; recurring attacks of abdominal pain and vomiting for 7 months; occult blood in stool; marked weight loss; lower jejunal obstruction and retention; resection; recurrence of obstruction; metastasis on laparotomy; death; no autopsy; total duration, 3 years	Carcinoma of lower jejunal area	Mesentary; peritoneum; liver
9	W. F., 72. Two years of epigastric distress aggravated by meals; death; autopsy; total duration, 2 years	Argentaffinoma of the upper ileum	Mesentery; peritoneum
10	W. F., 72. Cardiac disease; no gastrointestinal disturbance	Multiple; 3 argentaffinomas of the upper ileum and the jejunum	Mesentric nodes; peritoneum

Case No.	Clinical Features	Pathologic Process	Metastasis
11	W. M., 62. Cardiac disease; no gastrointestinal disturbance	Argetaffinoma of the middle ileum	Mesentery; liver
12	W. M., 44. Episodes of severe abdominal pain for 4 years, more severe and frequent for 4 months; no relation to meals; signs of perforation; operation; perforation of jejunum, general peritonitis; death; autopsy; total duration, 4 years	Multiple argentaffinomas of the lower ileum (7)	Cecal and aortic lymphatic nodes; peritoneum; liver
13	B. F., 51. "Gas pains" and diarrhea for 4 weeks; rectosigmoid obstruction; resection of ileum and colostomy; rectosigmoid obstruction from lymphopathia venereum	Argentaffinoma of the ileum	None
14	W. M., 58. Cardiac and prostatic disease; no gastrointestinal disturbance	Argentaffinoma of the ileum	None
15[1]	W.F., 46. Admitted in extremis; death in 8 hours; five year history of recurrent vomiting and diarrhea; later weight loss; autopsy; total duration, 5 years	Diffuse lymphosarcoma of the duodenum and jejunum	None
16	W. F., 60. Four year history of weakness, vomiting, distention and intolerence to fats; cholecystectomy two years later, with short free period; recurrence of nausea and vomiting; epigastric pain 1½ years; gradual weight loss; acute episode of perforation; laparotomy—perforation through tumor mass; resection; death; no autopsy; total duration, 4 years	Lymphosarcoma of the jejunum	?
17	Chinese M., 45. Acute onset of constant abdominal pain, vomiting, tarry stools, signs of peritonitis; operation; perforated jejunum; peritoneal metastasis; death; no autopsy	Lymphosarcoma of the jejunum	Peritoneum

*Previously reported by Lisa and others (case 2, J. Lab. & Clin. Med. **20**: 150, 1934).
†Dr. Russell H. Patterson gave us permission to include this case.
‡From the private practice of one of the authors (D. S. L.).
[1]Previously reported by Likely and Lisa (Am. J. Digest. Dis. & Nutrition **6**: 113, 1939 [case 2]) as a case of granulomatous tumor. Reexamination indicated that this diagnosis was incorrect.

TABLE 2.—*Statistical Incidence of Primary Malignant Growths of the Small Bowel*

Authors	Period, Yr.	Source	Carcinomas	Argentaffinomas	Lymphosarcomas*
Cameron3d	--	200 jejunal and ileal malignant growths	109	13	(78)
Morison1	10 10	13, 139 autopsies and operations Clinical records	4 2	2 1	4 (2)
Swenson 3c	--	50 malignant growths of the small bowel	22	4	15
Warren 3a	17	--------	17	4	2
Bottsford and Seibel 12a	34	Autopsies and operations	18	16	13
Likely and others	27	6,226 autopsies 23,776 surgical procedures others	4 2 2	5 1 --	1 2 --
Medinger3e	12	1,456 autopsies 41,000 operations	16	--	0
Morrison and Donath41a	--	25,631 autopsies and operations 28,390 admissions	10	--	2
Fraser 3f	10	22,970 operations 2,674 autopsies	6	--	(7)
Shallow and others 3b	--	--------	186	--	(83)
Emmet and Dreyfuss 12b	10	--------	11	--	(7)
Swan, J. M.: M. Times, New York 74:46-52 and 105-112, 1946	--	--------	258	--	13
Ehrlich and Hunter 12c	--	441 malignant growths of the gastrointestinal tract	9	--	2
Horsley3	9	Jejunum and ileum	243	141	--
Mayo and Nettrour	--	--------	76	--	--
Howard7	13	10,340 autopsies on patients with carcinoma 1,650 autopsies	152 5	-- --	-- --
O'Donoghue and others 45a	14	16,318 autopsies	7	--	--
Boman50	--	230,000 admissions	7	--	--
Ficarra and Marshall 27	30	--------	29	--	--
Porter and Whelan 33	28	--------	--	9	--
Dockerty and Ashburn 32	37	--------	--	30	--
Chont, L. K.: Radiology 36: 86-97, 1941	--	2,252 autopsies 20,603 operations	--	--	3
Sugerbarker and Craver 51a	20	196 lymphosarcomas	--	--	4
Menne and others39	--	11,446 autopsies 38,076 operations	--	--	1
Ritter and Shaffer 56a	13	--------	--	--	5
Frank and others 23	--	102 lymphosarcomas of the small large bowels	--	--	69
Usher and Dixon 21a	--	50 sarcomas of the small and large bowels	--	--	19
Kock 24k	41	Operative cases	--	--	7
Cutler and others 21b	10	--------	--	--	2

*Figures in parentheses include sarcomas other than the lymphoma tous type.

interesting to note that in our series, covering a period of twenty-seven years, 5 of the 6 cases were observed in the last six years.

Argentaffinoma of the small intestine has been reported with increasing frequency since the classic contribution of Forbus[16] in 1925. Gaspar[17] collected about 70 cases; other observers[18] increased the number to 332 by 1944. About 33 more have been reported since then,[19] to which can be added the present series. Probably, as Horsley[5] has stated, they are more frequent than commonly believed.

Lymphosarcoma of the small bowel, in contrast to carcinoma, is more frequent than that of the large bowel[20]; only a few reports[21] show the reverse. Its true incidence is difficult to estimate because of insufficient or obscure data in the reports and of conflicting figures.[22] Frank and others[23] found 361 cases of intestinal lymphosarcoma in the literature up to August 1942. Of the 102 in which a histologic diagnosis was made, 69 were cases of lymphosarcoma of the small intestine. Since then 80 cases, including the present series, have been reported.[24] In

16. Forbus, W. D.: Bull. Johns Hopkins Hosp. **37**:130-153, 1925.

17. Gaspar, P.: Am. J. Path. **6**:515-524, 1930.

18. (*a*) Ariel, I. M.: Argentaffin (Carcinoid) Tumors of Small Intestine: Report of Eleven Cases and Review of Literature, Arch. Path. **27**:25-52 (Jan.) 1939. (*b*) Dangremond, G.: Am. J. Clin. Path. **12**:223-231, 1942. (*c*) Ritchie, G., and Stafford, W. T.: Argentaffin Tumors of Gastrointestinal Tract, Arch. Path. **38**:123-127 (Sept.) 1944.

19. (*a*) Bonar, A. A.: Brit. M. J. **1**:391-392, 1946. (*b*) Watz, C. E.: Minnesota Med. **28**:558-559, 1945. (*c*) Blumgren, J. E.: ibid. **27**:620-623, 1944. (*d*) Korkosz, A.: Gastroenterology **1**:961-964, 1943. (*e*) Malignant Carcinoid of Ileum, Cabot Case 30241, New England J. Med. **230**:739-742, 1944. (*f*) McLeod, C. E.: Am. J. Clin. Path. **14**:301-303, 1944. (*g*) Stevenson, W. O., and Blanchard, A. J.: Canad. M. A. J. **51**:259-260, 1944. (*h*) Betancourt, P. I., and Vidauretta, Z. M.: Arch. cubanos cancerol. **3**:113-124, 1944. (*i*) Reynolds, R. P., and Cantor, M. O.: Am. J. Surg. **71**:705-709, 1946. (*j*) McNeely, R. D. G., and Jones, W. N.: Gastroenterology **6**:443-448, 1946. (*k*) Swenson.[3c] (*l*) Bottsford and Seibel.[12a]

20. (*a*) Windt, G. V.: Rev. Policlín. Caracas **14**:277-285, 1945. (*b*) Ulmann, A., and Abeshouse, B. S.: Am. Surg. **95**:878-915, 1932. (*c*) Raiford[2a] (*d*) Warren[3a] (*e*) Shallow, Eger and Carty[3b] (*f*) Ehrlich and Hunter.[12c] (*g*) Morison.[1]

21. (*a*) Usher, F. C., and Dixon, C. F.: Gastroenterology **1**:160-178, 1943. (*b*) Cutler, G. D.; Stark, R. B., and Scott, H. W.: New England J. Med. **232**: 665-670, 1945.

22. (*a*) Benjamin, E. L., and Christopher, F.: Am. J. Clin. Path. **10**:408-413, 1940. (*b*) Charache, H.: Am. J. Surg. **59**:601, 1943.

23. Frank, L. W.; Miller, A. J., and Bell, J. C.: Ann. Surg. **115**:544-565, 1942.

24. (*a*) Borden, D. L., and Taylor, F. D.: Mil. Surgeon **92**:255-257, 1943. (*b*) Dinsmore R. S., and Ancona, V. C.: Cleveland Clin. Quart. **11**:77-79, 1944. (*c*) Sanguily, J.: Arch. cubanos cancerol. **4**:170-176, 1945. (*d*) Berman, H., and Mainella, F.: Am. J. Surg. **70**:121-125, 1945. (*e*) Moreton, R. D.: Texas State J. Med. **41**:458-464, 1946. (*f*) Mascheroni, H. A.; Reussi, C., and Clerici, L. E.: Rev. Asoc. méd. argent. **60**:330-333, 1946. (*g*) Alsup, F. F.: Hawaii M. J. **5**:

(Footnote continued opposite page)

addition 3 probable cases have been reported.[25] Mena's case[26] may be one of an inflammatory lesion. There are probably about 200 authentic cases in the literature.

The site of predilection of carcinoma, argentaffinoma and lymphosarcoma, differs. In cases of carcinoma, each segment, i.e., duodenum,[27] jejunum[28] and ileum,[29] has been ranked first. Other observers[30] found no particular susceptibility of any segment. The statement of Morison,[1] however, appears justified: "For the area at risk, the literature does suggest that the highest incidence of carcinomata of the small intestine is in the duodenum." In the duodenum, the second portion is most likely to be affected.[30] The ileum is the favorite location for argentaffinoma and lymphosarcoma. Including the 69 cases of Frank and others[28] and the more recent cases in which the site is given, 15 cases of duodenal, 31 cases of jejunal and 68 cases of ileal lymphosarcoma have occurred. In 10 cases there was a multiple origin.

Carcinoma of the small bowel usually occurs in the form of a single lesion, tends to be stenotic, encircles the lumen and involves short segments. In some cases it is polypoid, fungating or pedunculated. Multiple carcinomas are rare. Histologically, it usually shows gland formation, scirrhous reaction and papillation. Adenoacanthoma is rare,[31] as is colloid carcinoma. Causal relation to duodenal ulcer is doubtful.[8]

Carcinoids are usually small submucous masses, firm in consistence, extending toward the mucosa, which frequently remains intact, and growing outward into the mesentery. Gross ulceration is uncommon, although small ulcers can be demonstrated frequently in the larger tumors on microscopic examination.[32] They occasionally are pedunculated. They tend to involve only a portion of the wall and do not

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197-198, 1946. (*h*) Svein, H. J., and Rivers, A. B.: Am. J. Digest. Dis. **9**:45-47, 1942. (*i*) Fritzsche, R.: Schweiz. med. Wchnschr. **73**:442-445, 1943. (*j*) Wybert, A., and Rodrigues, R. V.: Rev. Asoc. méd. argent. **55**:443-446, 1941. (*k*) Kock, W.: Acta chir. Scandinav. **89**:37-67, 1943. (*l*) Warren[3a] (*m*) Swenson.[3e] (*n*) Bottsford and Seibel.[12a] (*o*) Ehrlich and Hunter.[12c] (*p*) Footnote 21.

25. Montel, M. G.: Lyon chir. **37**:339-340, 1942. Colesanti, G.: Gazz. internaz. med.-chir. **47**:315-320, 1937. Windt.[20a]

26. Mena, R. I.: Rev. méd. de Chile **71**:800-803, 1943.

27. Ficarra, B. J., and Marshall, S. F.: S. Clin. North America **25**:713-718, 1945. Raiford.[2a]

28. Swenson.[3c] Mayo and Nettrour.[4]

29. Bottsford and Seibel.[12a] Fraser.[3f]

30. Berger, L., and Koppelman, H.: Ann. Surg. **116**:738-750, 1942.

31. Lieber, M. M.; Stewart, H. L., and Morgan, D. R.: Adenosquamous Carcinoma of Peripapillary Portion of Duodenum, Arch. Surg. **40**:988-996 (May) 1940.

32. Dockerty, M. B., and Ashburn, F. S.: Carcinoid Tumors (So-Called) of Ileum: Report of Thirteen Cases in Which There Was Metastasis, Arch. Surg. **47**:221-246 (Sept.) 1943.

encircle the circumference. A favorite location is at or near the mesenteric reflexion. The lumen of the intestine is slightly encroached on by the tumor but mainly deformed by angulation caused by growth into the mesentery. On section, the color is frequently yellow or gray, with yellow foci. Many times they are multiple, and they may occur in groups. The rate of growth is slow. The origin of the carcinoid is considered to be the Kultschitzky cells of Lieberkühn's glands. They form small homogeneous cell masses separated by fibrous septums. The cells are small, opaque and finely granular, have obscure borders and are chromophilic and argentophilic. The peripheral cells tend to be in palisade formation. Occasionally there are glands. The nuclei are round or oval and stain deeply. In morphologic pattern, carcinoids closely resemble basal cell carcinoma of the skin.

Lymphosarcoma appears to have a focal origin in lymphatic tissue[33] and may develop as the small cell type, malignant lymphocytoma, or the large cell type, reticulum cell sarcoma. In the small intestine it arises from the lymphatic tissue of the mucosa and submucosa. The tendency is toward diffuse invasion and outward growth into the wall and mesentery and longitudinally along the long axis. Usually it involves the entire circumference and a longer segment than that involved in carcinoma. It is more likely to cause dilatation of the lumen than stenosis, producing an aneurysmal small mass. Sometimes it is constricting and fungating. Ulceration is frequent. The tissue is homogeneous, fairly firm and gray. The tumor may be multicentric in origin. According to Cameron, [3d] one twelfth are of this nature.

Regional metastasis in carcinoma is said to occur early.[34] Howard[7] claimed that it was late, and Raiford[2a] found metastasis in only 25 per cent of his cases. Contiguity invasion of the pancreas is stated to be rare.[1] In our experience it has not been uncommon in duodenal lesions, and Howard's experience is similar. Distant metastasis is late.

Carcinoids of the small bowel have been classed as benign tumors,[35] but their tendency to metastasize justifies their inclusion among the malignant growths. Porter and Whelan[36] have shown that carcinoids of the gastrointestinal tract, other than appendical, have a definite tendency to metastasize. Dockerty and Ashburn[32] reported metastasis in 43 per cent of their cases. Usually it occurs only in the draining lymphatic vessels, but the liver is a fairly common site. Widespread

33. Stout, A P.: Is Lymphosarcoma Curable? J.A.M.A. **118**:968-970 (March 21) 1942. Ulmann and Abeshouse.[20b]

34. Rankin, F. W., in discussion on Horsley.[5] Fraser.[9f] Mayo and Nettrour.[4] Bottsford and Seibel.[12a]

35. Morison.[1] Raiford.[2a] Cohn. [2c] Forbus.[10]

36. Porter, J. E., and Whelan, C. S.: Am. J. Cancer **36**:343-358, 1939.

metastasis[37] is uncommon. The metastasis has the same slow growth as the primary lesion.

In lymphosarcoma, lymphatic metastasis apparently occurs early,[38] although Raiford[2a] stated that it occurs less readily than in carcinoma Hematogenous spread is uncommon.[39]

Persons with carcinoma and lymphosarcoma of the small intestine are predominantly male; there is no sex difference for carcinoids. The average age at which carcinoma occurs is the fifth decade. Carcinoids tend to occur among older persons. Fifty per cent of the cases of lymphosarcoma involve persons between 30 and 60 years of age[23] and 10 per cent involve infants and children.[40]

The symptoms of the three types of malignant growths of the small intestine have several features in common and certain differences. They are somewhat dependent on the site of the lesion, may be acute or chronic in onset and may be present for a variable period. The most characteristic symptom complex is that of intermittent obstruction.[41] With high tumors, vomiting occurs early.[3b] In suprapapillary carcinoma, acute onset is common and vomiting prominent.[42] The vomitus usually contains blood, free hydrochloric acid and gastric enzymes. The lesions of the second portion of the duodenum tend to give the same signs, with mild transient jaundice. In infrapapillary lesions, there are obstructive symptoms, gastric upsets and vomitus which contains blood, bile, hydrochloric acid and gastric and pancreatic enzymes. Gastric upsets are less noticeable and more transient[3b] and sometimes are manifested only by unexplained mild nausea[5] when the lesions are lower in the tract.

Anemia is common in cases of carcinoma and sarcoma and extremely unusual in cases of carcinoid. Massive hemorrhage is not frequent, although the stool usually contains occult blood, except when carcinoid is present. Easy fatigability is usually associated with the anemia.

Pain is almost invariable in sarcoma,[43] and is common in carcinoma, and it is usually cramplike during periods of obstruction.

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37. Porter.[3a] Watz.[19b]

38. Ulmann and Abeshouse.[30b] Usher and Dixon.[21a]

39. Meune, F. R.; Mason, D. G., and Johnston, R.: Lymphosarcoma of Intestine: Report of Two Cases, Arch. Surg. **45**:945-956 (Dec.) 1942.

40. Cameron.[3d] Frank, Miller and Bell.[23]

41. (*a*) Morrison, W. A., and Donath, D.: California & West. Med. **55**:235-237, 1941. (*b*) Swenson.[5c] Bottsford and Seibel[19a] Emmet and Dreyfuss.[12b] Frank, Miller and Bell.[23]

42. Cohn.[14] Berger and Koppelman.[30]

Change of bowel habits is usually manifested by constipation, apparently coinciding with obstruction. Alternating diarrhea and constipation seem to be late and do not occur frequently.

Loss of weight occurs early in sarcoma, is usually late in carcinoma and is absent in carcinoid.

Palpable tumor is more common when the lesions are of the lower segments. It is frequent in sarcoma[43] and in jejunal and ileal carcinoma and occasionally present in carcinoid.

Intussusception, usually due to benign lesions,[44] is frequent in sarcoma and uncommon in the other two malignant growths. It may occur with pedunculated tumors.[45] Perforation is uncommon but occasionally occurs.[46] Pellagrous[19j] and spruelike syndromes[47] are rare manifestations.

Cases of carcinoma[48] and sarcoma[2a] in which the patients are symptom free are uncommon. Silent carcinoids are more frequent.[49]

The prognosis is considered poor in cases of carcinoma[50] and sarcoma[51]; it is good in cases of carcinoid.[52] Cameron[3d] stated that the five year survival rate in the first two types is less than 5 per cent. Of the carcinomas, jejunal and ileal lesions carry a more favorable prognosis than duodenal lesions.[53] The sarcomas carry a more favorable prognosis[54] than the carcinomas. The prognosis depends somewhat on the presence or absence of metastasis in carcinoma and sarcoma[55] but not in carcinoids. The slow growth of carcinoids does not tend to shorten life. However, there have been reported several cases in which there was a long survival even after operation for more malignant tumors.[56] Most of these have been reported in the later years, which suggests that the prognosis in the future may not be so hopeless as early experience denoted.

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43. Bottsford and Seibel.[12a] Ulmann and Abeshouse.[20b]

44. Fiske, F. A.: Ann. Surg. **106**:221-229, 1937.

45. (*a*) O'Donoghue, J. B.; Lichtenstein, M. E., and Jacobs, M. B.: Am. J. Surg. **63**:382-387, 1944. (*b*) Black, B. M.: Proc. Staff Meet., Mayo Clin. **19**: 142-146, 1944. Korkosz.[19d]

46. Fraser.[3f] Kock.[24k] Korkosz.[19d] McLeod.[19f]

47. Swenson.[5c] Fritzsche.[24l]

48. Swenson.[5c] Ruden.[9] Felson and Wolarsky.[10]

49. Bottsford and Seibel.[12a] Porter and Whelan.[28] Ariel.[18a] Dangremond.[18b]

50. (*a*) Boman, P. G.: Ann. Int. Med. **20**:779-788, 1944. (*b*) Raiford.[8a] (*c*) Warren.[5a] (*d*) Bottsford and Seibel.[12a] (*e*) Black.[45b]

51. Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma: Study of One Hundred and Ninety-Six Cases with Biopsy, J.A.M.A. **115**:17-23, (July 6); 112-117 (July 13) 1940 (*b*) Cameron.[3d] (*c*) Usher and Dixon.[21a] (*d*) Kock.[24k]

52. Warren.[5a] Ariel.[18a] Dockerty.[22] Footnote.[19e]

53. Shallow, Eger and Carty.[7b] Medinger.[8e]

54. Shallow, Eger and Carty.[7b] Ulmann and Abeshouse.[20b]

55. Howard.[7] Rankin.[24]

Roentgenologic examination is a most valuable procedure in the diagnosis of malignant growths of the small bowel. The criteria are the same as those used for the diagnosis of tumors in the large bowel[57] and give evidence of the gross nature of the lesion.[58] It is worth noting, however, that growths of equal size in the colon produce a more definite type of picture. Plain roentgenograms sometimes prove of value if they indicate obstruction.[12a]

Therapy is radical resection, with removal of draining lymph nodes. For argentaffinomas, this is indicated even in the presence of metastasis to the liver. Postoperative irradiation has been used in some cases of lymphosarcoma and not in others, with identical long survival periods.

SUMMARY AND CONCLUSIONS

Seventeen cases of malignant growth of the small bowel are reported, and the recent literature is reviewed. They are of uncommon occurrence. Certain clinical features suggest the possibility of their presence. Intermittent obstruction is a common manifestation. In some cases the presenting symptom is mild unexplained nausea. In the presence of anemia of gastrointestinal origin for which no adequate explanation is found on examination of the stomach and large bowel the small bowel should be thoroughly investigated. The prognosis is usually considered poor in cases of carcinoma and lymphosarcoma and good in cases of argentaffinoma. The more recent literature suggests that the prognosis may depend largely on early diagnosis rather than on the type of tumor, particularly in reference to carcinoma and lymphosarcoma. Roentgenologic studies are most valuable. The therapy is radical resection. Awareness of the possibility of the existence of the condition remains the prime necessity for early diagnosis.

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56. (*a*) Ritter, H. H., and Shaffer, J. M.: Am. J. Surg. **55**:611-612, 1942. (*b*) Horsley.[5] (*c*) O'Donoghue.[45a] (*d*) Shallow, Eger and Carty.[5b] (*e*) Swenson.[5c] (*f*) Morison.[1] (*g*) Fraser.[9f] (*h*) Medinger.[5e] (*i*) Ulmann and Abeshouse.[20b] (*j*) Berman and Mainella.[24d] (*k*) Charache.[22b] (*l*) Alsup.[24g] (*m*) Warren.[3a] (*n*) Usher and Dixon.[21a]

57. Good, C. A., and McCarthy, W. E.: Proc. Staff Meet., Mayo Clin. **17**: 20-22, 1942. Good.[5b]

58. Weber, H. M., and Kirklin, B. R.: Am. J. Roentgenol. **47**:243-253, 1942.

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CONTENTS

PAGE

Acute Diffuse Interstitial Fibrosis of the Lungs: Report of a Case. BENJAMIN P. POTTER, M.D., AND ISADORE E. GREENE, M.D., JERSEY CITY, N. J. 113

Clinical Experience with Nitrogen Mustard Therapy. R. GOLDMAN, M.D.; R. O. EGEBERG, M.D.; E. R. WARE, M.D.; E. R. EVANS, M.D., AND B. G. FIRSKIN, M.D., LOS ANGELES 125

Osteopetrosis. LIEUTENANT (JG) WILLIAM J. CASSIDY, MEDICAL CORPS, UNITED STATES NAVAL RESERVE; FRANCIS C. ALLMAN, M.D., WASHINGTON, D. C., AND LIEUTENANT (JG) GERALD J. KEEFE, MEDICAL CORPS, UNITED STATES NAVAL RESERVE 140

Association of Hepatic Insufficiency with Chronic Ulcerative Colitis. H. MARVIN POLLARD, M.D., AND MALCOLM BLOCK, M.D., ANN ARBOR, MICH. 159

Study of Tremor in Soldiers. JACOB J. SILVERMAN, M.D., WITH THE TECHNICAL ASSISTANCE OF RUDOLPH STEIN, STATEN ISLAND, N. Y. 175

Pernicious Anemia in the Tropical Negro. CAPTAIN SIDNEY P. ZIMMERMAN AND CAPTAIN SHELDON DUGGER, MEDICAL CORPS, ARMY OF THE UNITED STATES 184

Clinical Observations in Cases of Massive Myocardial Infarction. ARTHUR SELZER, M.D., SAN FRANCISCO 196

Primary Malignant Disease of the Small Bowel. DAVID STANLEY LIKELY, M.D., AND JAMES R. LISA, M.D., NEW YORK; MELVIN H. STITCH, M.D., BROOKLYN, AND H. D. STEIN, M.D., ELKINS PARK, PA. 206